Mixing and formulation factors influencing the dissolution of phenytoin sodium

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MIXING AND FORMULATION FACTORS

INFLUENCING THE DISSOLUTION OF

PHENYTOIN SODIUM

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DEDICATION

To my parents

ABSTRACT

Phenytoin sodium often shows irregular release and absorption behaviour which is often linked to the dissolution characteristics of the drug from a dosage form. In this study, the in-vitro release of the drug from single and multi-component capsule formulations has been studied in borate buffer pH 9.0 using the USP paddle method at 50 rpm. The dissolution rates from various formulations have been compared by using either the percentage drug dissolved in 30 minutes or by calculating the dissolution rate constants according to the method of Kitazawa et al (1977).

The release of particulate drug alone was fast and was generally retarded by the addition of both soluble and insoluble diluents. These diluents retarded dissolution rate by facilitating the precipitation of the free insoluble acid form during dissolution. The amount precipitated depended on the diluent concentration and solubility, and also the diffusion layer pH around a soluble diluent. Formulations containing soluble diluents with low diffusion layer pH showed slower dissolution. Also, the greater the extent of physical surface interaction between drug and diluent particles the greater the retardation observed. The dissolution rate also depended on the diluent particle size; the effect was attributed to the probable pore size distribution within the capsule powder bed.

For three-component formulations containing either lactose or calcium sulphate, the effect of batch-to-batch variation in magnesium stearate depended on the specific surface area of the lubricant; formulations containing lubricant of high specific surface area showed slower dissolution rates. Drug release was also greatly modified by changes in the spatial arrangement of particles which could be altered

by changing either the chemical type or source of diluent, the lubricant concentration, or the mixing sequence of the components. Such changes in the spatial arrangement of particles were identified by means of semi-quantitative analysis of ordered units in powder mixes using SEM combined with X-ray analysis.

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1. INTRODUCTION

1.1 SOLID ORAL DOSAGE FORMS - CAPSULES

Solid oral dosage forms are medication delivery systems presented as solid dose units readily administered by mouth (Marshall, 1979). They include tablets, capsules, cachets, pills as well as bulk or unit dose powders or granules. The most popular forms are tablets and capsules. With capsules, the drug is enclosed either as powder in a hard gelatin shell or as liquids or pastes in hard or soft gelatin shells. A hard gelatin shell consists of two parts, the body and a cap which fits over the open end of the body. They are available in various sizes to accommodate various powder weights. Powders which are to be filled into hard gelatin capsules have to be modified and/or formulated individually to fulfil the appropriate specification and end use of the product. On the one hand the powder system must be capable of easy and precise division into equal amounts for filling into capsules, while on the other hand the system must disintegrate and release drug as required. To achieve these primary objectives, the physicochemical characteristics of the drug must first be well defined in a preformulation study. Formulation studies must then be undertaken to identify the preferred excipients such as diluents, lubricants and disintegrants which must be mixed with the drug to obtain the final desired dosage form.

1.2 PHENYTOIN

1.2.1 General

Phenytoin is the approved name for 5,5-diphenylhydantoin or 5,5-diphenyl-2,4, -imidazolidinedione (Chemical Abstract name). The compound's structure is shown in Fig. 1.1a, as the free acid and Fig. 1.1b, as the sodium salt.

Phenytoin is the hydantoin derivative which has been most widely used in medicine, mainly in the treatment of epilepsy. It is most useful in the treatment of grand mal and psychomotor seizures but of little value in petite mal, myclonic seizures and absences. The drug is also useful in the treatment of cardiac arrythmias, migraine, trigeminal neuralgia and certain psychoses. Side effects of phenytoin therapy are of fairly frequent occurrence and include unpleasant effects such as nausea, vomiting, coarsening of facial features, acne, hirsutism. Overdosage may lead to hypotension, coma and respiratory depression. (Martindale, 1982)

The free acid form is used in aqueous suspensions and also in formulating chewable tablets. The sodium salt is often presented in capsules though some tablet formulations exist. Recommended doses range from 50mg to 200mg (sodium salt) three times a day.

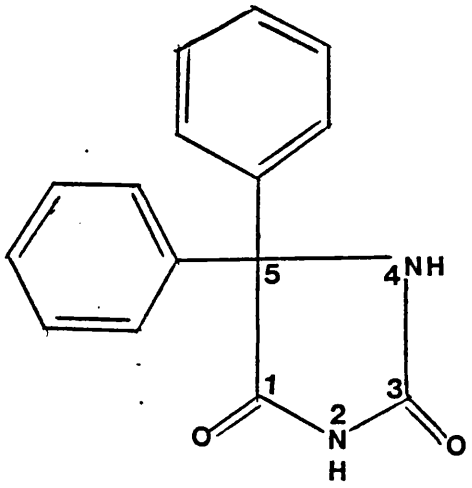
1.2.2 Problems of bioavailability

Although phenytoin has long been used in anticonvulsant therapy, there are still difficulties with its frequent use and many patients are not consistently and adequately controlled (Edwards, 1984). The problem of phenytoin therapy is linked to a wide variety of factors which are inter-related but three main reasons have been identified. These are:-

Fig.1.1 Chemical structure of (a) Phenytoin

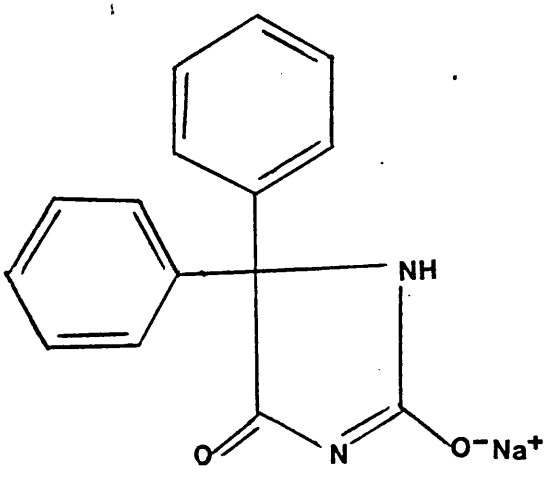
(b) Phenytoin sodium

(a)



MWT = 252.3

(b)



MWT = 274.3

(1) Non-linear pharmacokinetics

(2) Narrow therapeutic range

(3) Variable gastro-intestinal absorption from oral dosage forms.

1.2.2.1 Non-linear pharmacokinetics and narrow therapeutic range

Phenytoin is hydroxylated to 5-(p-hydroxyphenyl)-5 phenylhydantoin, p-HPPH, (Butler, 1957) by the microsomal mixed function oxidase enzymes in the liver.

The elimination of the drug has been shown to exhibit non-linear pharmacokinetics where there is no simple relationship between dosage and serum levels of drug. (Bochner et al, 1972a; Gugler et al, 1976). Two theories have been proposed to explain this, but the most widely accepted is the capacity-limited or saturation kinetics of the enzyme system. This theory explains that at very low concentrations, the enzyme system is dose-dependent and drug elimination follows first order kinetics where the elimination rate increases as the dosage is increased. At higher doses, a point is reached when the enzyme system becomes saturated. Drug metabolism is then limited and the drug begins to accumulate in the blood. The metabolism at this point becomes zero-order and as a result the relationship between dose and blood serum levels is non-linear.

It has been found that for adequate control of epileptic seizures blood levels of 10-20μg/ml must be achieved (Lund, 1974a). Higher blood levels are often associated with toxic side effects such as somnolence, confusion and nystagmus. Lower blood levels are often sub-therapeutic though some patients may be adequately controlled with serum levels of 8 or 9μg/ml. However, the saturation of the

enzyme system can occur even in this narrow therapeutic range and a dosage increase from say, 300mg to 400mg may take a patient from sub-therapeutic to toxic drug concentrations (see Fig. 1.2).

The second explanation, proposed by Glasko (1972) to explain the non-linear kinetics discussed above, is based on the inhibition of phenytoin's hydroxylation to p-HPPH (Borondy, Chang and Glasko, 1972). He postulated that the inhibition was caused by a feed-back mechanism where accumulating p-HPPH competed with phenytoin for binding sites on the enzyme complex leading to high drug levels. He explained further, that the build-up of p-HPPH occurred because the conjugation of the p-HPPH with glucuronic acid and its subsequent elimination was a rate-limiting step. Levy and Ashley (1973) also came up with a similar hypothesis of product inhibition of the metabolism of phenytoin by accumulating metabolite p-HPPH, when an inhibitor of glucoronide formation was given to rats. Peruca and co-workers (1978) tested this theory but found no evidence to suggest a feed-back mechanism. Clearly more work is needed in this area to prove or disprove the hypothesis.

1.2.2.2 Gastro-intestinal absorption

The oral route is the most popular and convenient route of drug administration for those drugs that can withstand the acid environment of the stomach and be absorbed across the gastro-intestinal tract (g.i.t.).

For most drugs absorption occurs by the passive diffusion of the lipid soluble unionised species, though an active uptake mechanism is involved for certain compounds. The diffusion mechanism is partly described by the pH-partition theory where the g.i.t. is assumed

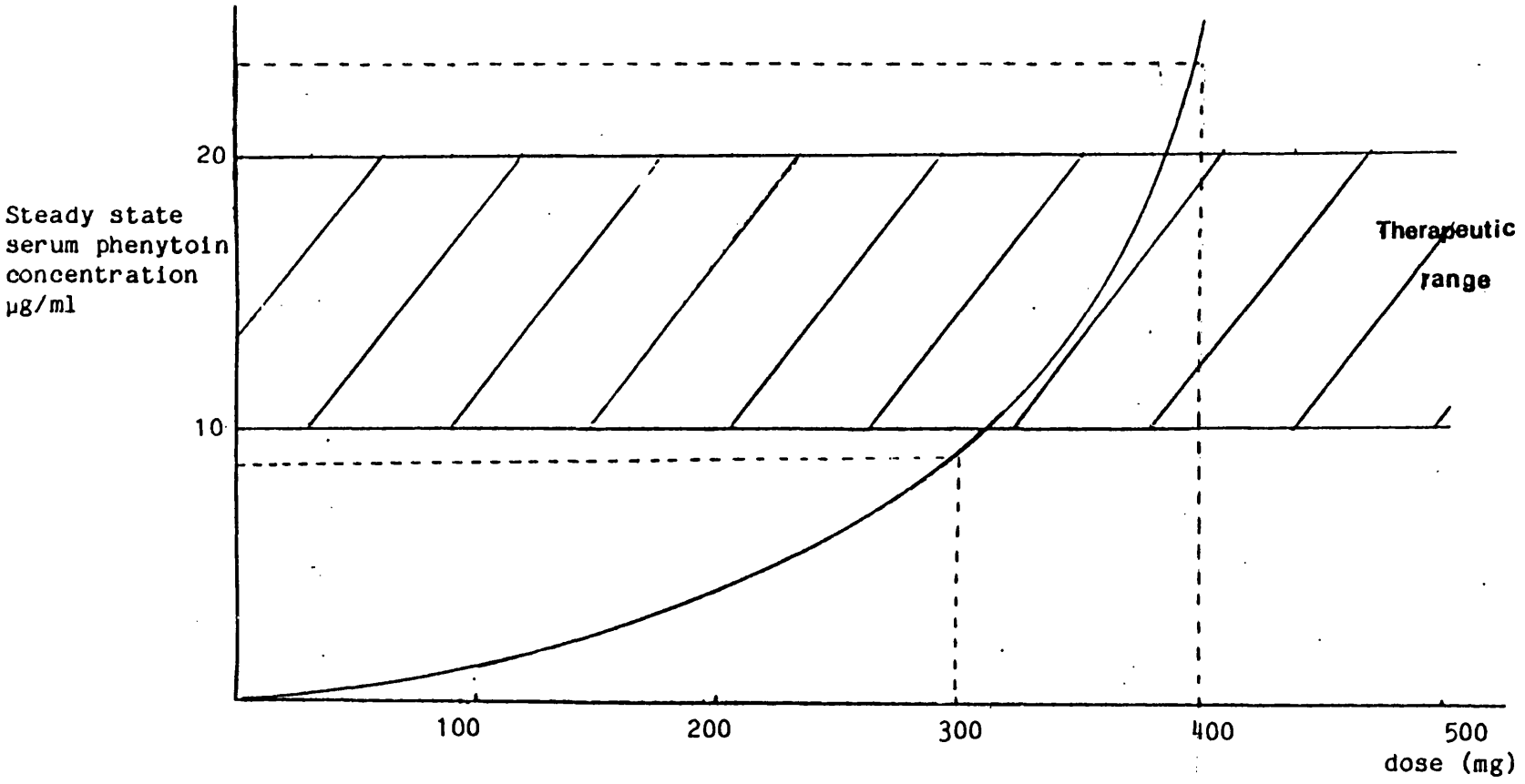


Fig 1.2 The Saturation Kinetics of Phenytoin

to be a simple lipid barrier and the non-ionised form of drugs, if sufficiently lipid soluble, may be absorbed. Most drugs are either acids or bases and the concentration of the non-ionised drug present in the g.i.t., is controlled by the apparent dissociation constant pka′ of the acid or base and also the pH of the g.i.t. according to the Henderson-Hasselbach equation. Thus for acids

$$pH = pka' + \log \frac{\text{ionised concentration}}{\text{un-ionised concentration}} \qquad \text{Equation 1.1}$$

and for bases,

$$pH = pka' + \log \frac{\text{un-ionised concentration}}{\text{ionised concentration}} \qquad \text{Equation 1.2}$$

Generally very weak acids with pka′ greater than 8 are essentially un-ionised in the stomach, where the pH is very low(1-2.5; Scientific Tables), and may easily be absorbed. Conversely, weak bases with pka′ less than 5 are largely un-ionised in the small intestines where the pH is higher. A few exceptions to the pH-partition hypothesis occur. Certain drugs, for example, quarternary ammonium compounds, may be absorbed in the ionised form but the exact mechanism by which this occurs is not yet known (Rowland and Tozer, 1980; Gibaldi, 1984).

For absorption to occur, drug molecules must be in solution at the surface of the gastro-intestinal membrane. When the formulation is administered in a form such as an elixir, aqueous solution or a syrup, the drug is already present in solution and the rate of absorption may be controlled by the rate of gastric emptying. In the case of solid dosage forms, for example tablets, capsules or even suspensions, the drug must first dissolve to be absorbed. The

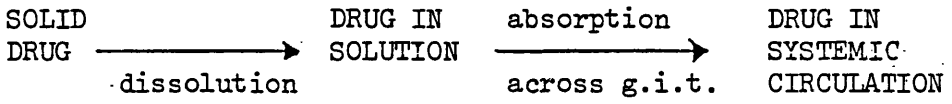
ability of the drug to go into solution or the rate of dissolution will depend on the physico-chemical character of the active drug and the way in which it is formulated.

Phenytoin is a weak acid and the pka' has been found by Schwartz et al (1977) based on solubility measurements in water as 8.06. That implies that 50% of the drug is ionised at pH 8.06. Earlier workers using UV spectrophotometry, potentiometric titrations in hydroalcoholic solutions (Agarwal and Blake, 1968) and titrations in 50% methanol (Dill et al, 1956) reported pka' values of 8.31, 8.33 and 9.2 respectively. Phenytoin is also practically insoluble in water with a solubility of only 21.9µg/ml at pH 7.5, 25°C and 18.4µg/ml at pH 4.9 (Schwartz et al, 1977). At higher pH, the drug is more soluble with a solubility of about 165µg/ml at pH 9.1 (borate buffer), and 1.52mg/ml at pH 10 (Dill et al, 1956).

Ideally if the drug were formulated as a solution the highly acidic environment of the stomach would limit the ionisation of the weak acid and favour passive absorption of the non-ionised drug. With its extremely low solubility at low pH, it is likely that precipitation of the acid may occur. However, experiments with other drugs suggest that these precipitates are usually finely divided and therefore easily redissolve to maintain saturation as the drug is removed from solution by absorption. Nevertheless, when phenytoin is administered in the solid state, the pH of the stomach will limit the ability of the drug to dissolve from the dosage form. Most absorption of the drug occurs in the proximal part of the small intestine, where the pH is higher and the presence of bile salts, which facilitate wetting and solubilisation of the drug, raises the drug's solubility, though the solubility is still very low. For a

drug such as phenytoin, the dissolution from the solid dosage form constitutes a rate-limiting step in the sequence of events leading to absorption (Fig. 1.3).

Fig. 1.3 Sequence of events leading to absorption of drug



Absorption is then said to be dissolution-rate-limited.

In addition to this problem, because of the non-linear pharmacokinetics, the steady state serum concentration is extremely sensitive to small differences in the total amount of drug absorbed as absorption approaches completeness (Rowland, 1981). Therefore, formulation factors, even those which exert only a slight influence on the ability of the drug to dissolve, may cause significant differences in the bioavailability of drug from dosage forms. This problem is particularly difficult since these differences are not detected in single dose trials but only become apparent during chronic clinical use of the drug as the steady state serum level may take a week or even up to 30 days to respond to dosage change (Ludden et al, 1978).

It is not surprising that reports of therapeutic inequivalence of phenytoin products arising from different dosage forms, different manufacturers and different sources of the drug have been widely reported in the literature. Therapeutic inequivalence has been reported in Sweden (Lund, 1974b), Finland (Pentikainen et al, 1975; Neuvonen et al, 1977), U.K. (Stewart et al, 1977), Chile (Cid et al, 1981), U.S.A. (Melkian et al, 1977), Canada (Arnold, Gerber and Levy,

1970), West Germany (Rambeck et al, 1977), China (Ma et al, 1983), Japan (Yahaba et al, 1981), Australia (Tyrer et al, 1970); Manson et al, 1975), Austria (Nitsche et al, 1984), India (Baichwal and Tipnis, 1981). A report by the Ad Hoc Committee on Drug Product Selection of the Academy of General Practice of Pharmacy in the U.S.A. labelled phenytoin as a drug with a high risk potential for therapeutic inequivalence. In-vitro dissolution tests have since been introduced in the United States Pharmacopoeia (USP, 1980) as a standard specification for phenytoin sodium capsules and to reduce the incidence of therapeutic inequivalence. The tests are carried out using the USP rotating paddle method at 50 r.p.m. in 900ml distilled water at 37°C. Limits have been defined for the amount of drug released at stated times. For prompt phenytoin sodium capsules, not less than 85% of the labelled amount of drug is dissolved in 30 minutes. Also, for the extended phenytoin sodium capsules not more than 40% is dissolved in 30 minutes, 50% in 60 minutes and not less than 70% in two hours. The capsules must also fall within the acceptance limits stated in the Pharmacopoeia/National Formulary (USP/NF, 1985). The differences in dissolution profile of phenytoin products were found by Shah and co-workers (1983a) to manifest themselves in in-vivo performance as significant differences in the rate but not in extent of bioavailability. The original Parke-Davis phenytoin sodium capsule has been found to be a slower release product than other products available. (Baichwal and Tipnis, 1981; Shah et al, 1983a,b).

In the British Pharmacopoeia (BP, 1980), a list of drugs has been given where clinical problems may arise if the required dose of drug is not made available, or if the physical characteristics of the drug may give rise to problems, or if there have been allegations of

bio-inequivalence. Perhaps surprisingly, phenytoin has not been included though there have been reports of inequivalence of phenytoin products in the U.K. Recently, a multiple cross-over study of Epanutin (Parke-Davis) capsules and 4 other generic tablets of phenytoin sodium available on the market showed significant differences in the bioavailability of the products but the magnitude was small and unlikely to cause clinical effect on alteration of therapy (Chen et al, 1982). Hirji et al (1985) also compared 5 different preparations of phenytoin available in Britain (Phenytoin tablets - Boots, Phenytoin tablets sugar coated - Evans Medical Ltd., Phenytoin sodium tablets - Thomas Kerfoot & Co., Phenytoin tablets - Cox & Co. Ltd and Phenytoin capsules BP - Parke-Davis). No significant differences were observed and the absolute bioavailability varied between 68-74%. It is also interesting that, in the USP, dissolution tests are specified for phenytoin sodium capsules but not for phenytoin tablets.

Other factors which may influence the absorption of phenytoin include the presence of food, concurrent administration of drugs (Kutt, 1975) and the disease state of the patient.

1.2.3 Dissolution : Factors influencing dissolution of phenytoin

The general progress in formulation design, the ability to anticipate absorption problems and the establishment of useful in-vitro dissolution tests have improved greatly the understanding of factors which control dissolution.

In order for dissolution of drug to occur from the solid state, molecules must escape from the surface of the solid and be transported away from the surface into the bulk solvent. Three

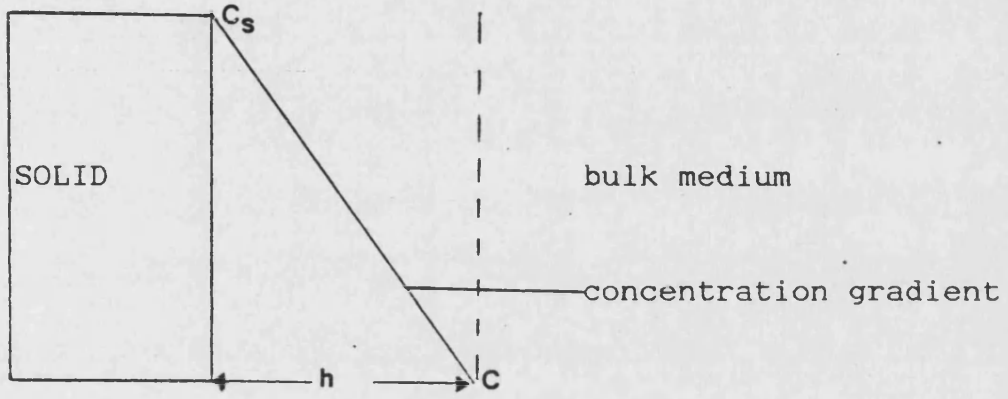
different models have been proposed to describe this process: the diffusion layer hypothesis, the interfacial barrier theory and Danckwerts model (Higuchi, 1967). In the diffusion layer model (Fig. 1.4a), a static layer of solvent is assumed to exist adjacent to the solid surface through which solute molecules diffuse along a concentration gradient into the bulk solution. The reaction of the solid at the surface of the liquid, occurs very rapidly and the rate of dissolution is determined primarily by the diffusion rate across the static film. The interfacial barrier model (Fig. 1.4b), proposes that the reaction at the solid surface is not instantaneous due to the high energy of activation required. Thus the process at the solid/liquid layer is rate determining and governs the rate of dissolution observed. In the third model, the Danckwerts model (Fig. 1.4c), the dissolution rate is assumed to be governed by the rate of transport of solute molecules by macroscopic pockets of solvent which attach themselves to free solid surfaces. These pockets are continually being replaced by fresh solvent molecules.

According to Higuchi (1967), the three processes described above may occur either alone or in combination with each other. The slowest process determines the overall dissolution mechanism. In the simplest case, the dissolution process may easily be explained by the diffusion layer model. In this model, when dissolution occurs from a planar surface and agitation conditions are low, the surface area of the dissolving solid remains constant and the dissolution rate depends on the concentration gradient between the saturated diffusion layer and the bulk fluid. This is given by the Noyes-Whitney (1897) equation:

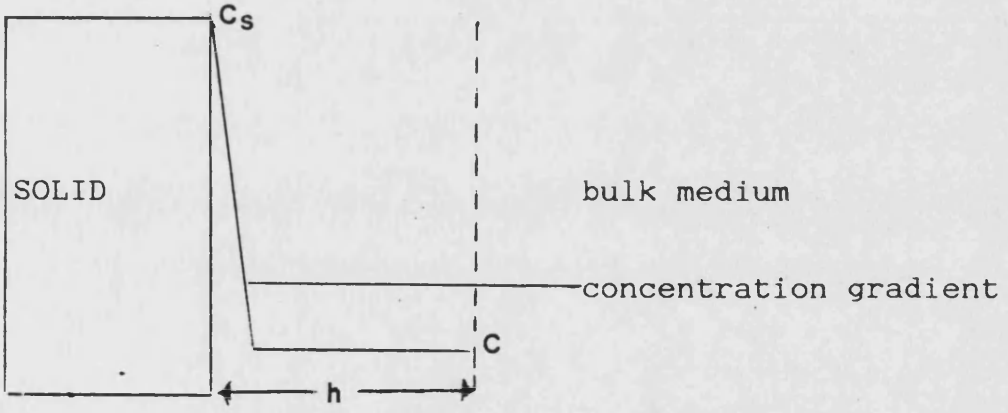
Fig. 1.4 Mechanisms of dissolution: (a) diffusion layer model
(b) interfacial barrier model
(c) Danckwerts model

C_s, is the solubility of the solid; C, concentration of the solid in the bulk medium and h, the thickness of the liquid layer

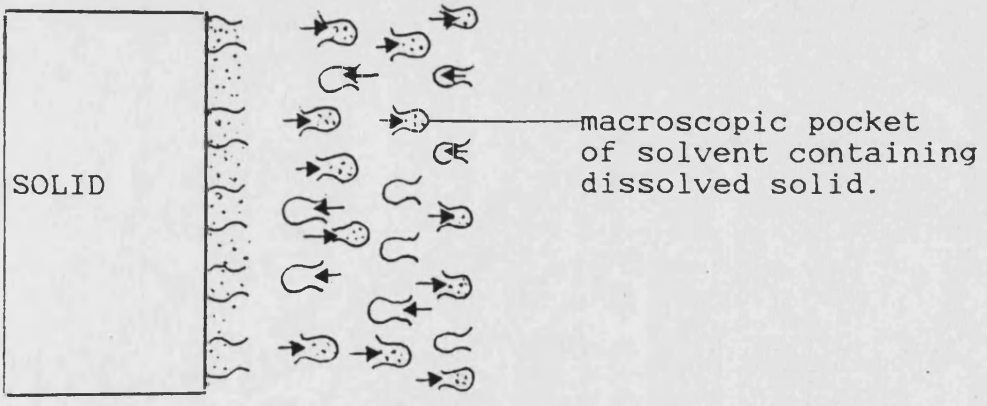
(a)



(b)



(c)



$$\frac{dC}{dt} = K (C_s - C) \qquad \text{Equation 1.3}$$

where: $\frac{dC}{dt}$, is the change in concentration of the solid in solution with time;

C_s, is the solubility of the solid;

C , the concentration of the drug in the bulk medium and K, a constant.

The constant K, can be expressed as (Nernst & Brunner,1904):

$$K = \frac{DS}{Vh} \qquad \text{Equation 1.4}$$

where D, is the diffusion coefficient of the dissolving solid;

h, the thickness of the static layer; S, the surface area of the solid and V, the volume of the dissolution medium.

The rate of dissolution, $\frac{dm}{dt}$, may then be expressed as:

$$\frac{dm}{dt} = \frac{dC}{dt} \cdot V = \frac{DS}{h} (C_s - C) \qquad \text{Equation 1.5}$$

When absorption of drug <u>in-vivo</u> is limited by the dissolution step, the dissolved drug in the g.i.t. content is continually removed by absorption from solution as dissolution occurs.

The bulk concentration, C, then remains very low and C_s is much greater than C. Under these sink conditions, the equation simplifies to:

$$\frac{dm}{dt} = \frac{DS}{h} C_s \qquad \text{Equation 1.6}$$

This equation may be used to explain most of the factors that influence dissolution.

In <u>in-vitro</u> tests, the experimental conditions influence the dissolution rate. The factors involved have been discussed by Rees (1977) and may be summarised as follows:-

(1) Intensity of agitation, type of flow, shape of dissolution vessel, etc.

(2) Concentration gradient or the difference between the concentration of the drug in the bulk fluid and its solubility in the dissolution medium

(3) Properties of the medium such as pH, ionic strength, viscosity, volume, etc.

(4) Temperature of the test which is normally carried out at body temperature, 37°C.

Usually, in-vitro test conditions may be adjusted to establish correlation between in-vitro test results and pharmacokinetic parameters such as time to peak in the blood, t_{max}; area under the blood concentration versus time curves, AUC, peak blood concentration, C_{max}. These parameters may be calculated from experimental plots which show the change in drug concentration in the blood (or plasma or serum as appropriate) with time. Good correlations have been observed for a variety of phenytoin products between the percentage of drug dissolved in 30 minutes and bioavailability measured by C_{max} and AUC values. The dissolution was carried out by the rotating basket method (USP) at 150 r.p.m. in borate buffer pH 9 (Brandau and Wehnert, 1979). Shah and others (1983a) have also reported good correlations between C_{max}, t_{max} and the percentage of drug dissolving in 30 and 60 minutes using the rotating basket method. Though it may be ideal to obtain correlations such as these, it is not always required for dissolution testing. Often the most important consideration is the ability of the test to provide meaningful quantitative screening of dosage forms. The observed differences, if any, are usually a result of variation in

drug properties, formulation and processing conditions which are considered below.

1.2.3.1 Crystal form and crystal habit

Many drugs can exist in more than one crystalline form a property known as polymorphism. The polymorphs show differences in space-lattice arrangements and also in certain physical properties such as density, melting point, solubility and sometimes dissolution rates.

Chakrabarti et al (1977) have recorded two crystalline forms of phenytoin which were either plate or needle-shaped. The plate form showed slightly higher dissolution rates for comparable particle sizes. No further work has been done to show if these differences may cause significant differences in bioavailability. The difference in dissolution of the two crystal forms has been suggested as due to active corners on the crystal edges and corners as well as points of crystal defects (Chakrabarti et al, 1978). Grabowska and Kaliszan (1974) have found that phenytoin precipitated from an aqueous solution of the sodium salt lost 0.5 mole of water at 185-190°C. A similar endothermic peak was observed for the plate form of phenytoin studied by Chakrabarti et al, (1978). The X-ray powder patterns for the two forms showed very little differences. It has been suggested that the differences were due to the presence of solvent and therefore it is likely that the solvent molecule played very little role in the crystal structure and probably occupied voids. This type of polymorphism is referred to as crystal pseudopolymorphism.

Solid materials may also be amorphous where the molecules are arranged in a random order, somewhat like in the liquid state. Because there is no ordered regular structure, amorphous materials require less energy to be solvated and dissolved, thus they show much higher dissolution rates than their crystalline polymorphs. Amorphous forms of phenytoin are formed during the preparation of solid dispersions or intensive mixing of crystalline phenytoin with polymer. These forms show much higher dissolution rate as predicted. However, Tammisto et al (1976) have documented an amorphous form of phenytoin which interestingly showed very low bioavailability, when formulated as a tablet, as compared to other tablets containing crystalline phenytoin.

Crystal habit of particles may be modified by changes in conditions during crystallization. Kwashima et al (1986) have prepared phenytoin crystals with improved flow, mechanical strength, dissolution rate and bioavailability by spherical crystallization. An alkaline solution of phenytoin at 40°C was added to a well dispersed mixture of isopropyl acetate and hydrochloric acid containing a water soluble polymer. Polymers used were polyvinyl-pyrrolidone, polyethylene glycol 4,000 or gelatin. Crystals produced were spherical in shape with smooth surfaces.

1.2.3.2 Surface area and particle size

From the Noyes-Whitney equation, the rate of dissolution is directly proportional to the surface area of solid exposed. Formulation scientists have often used this relationship to improve the dissolution of poorly soluble drugs by reducing the drug particle size. Classical examples are the improvement in bioavailability for formulations containing micronised griseofulvin and digoxin. As the size of a

particle decreases, its solubility also increases. A number of expressions have been developed to relate particle solubility to the particle characteristics. The most common is the Ostwald-Freundlich equation:

$$\log S/S_o = \frac{2\sigma_m M}{2.303\ \rho RT}\cdot\frac{1}{r} \qquad \text{Equation 1.7}$$

where S, is the solubility of the particle whose particle size has been reduced to radius r; S_o, the nominal solubility of a large particle; σ_m, the surface free energy of the crystal particle; M, the molecular weight and ρ, the density of the material. The increase in solubility is usually only significant when the particle diameter is reduced below 1μm.

It has been shown by a number of workers that the reduction of particle size improved greatly the dissolution rate of phenytoin (Johansen and Wiese, 1970; Johansen, 1972; Chakrabarti et al, 1977; Neuvonen et al, 1977; Yakou et al, 1984). However, attempts at correlating serum levels and particle size have shown some confirmatory and other contradictory results. A study to correlate particle size and bioavailability performed in dogs reported that the AUC was inversely related to particle size (Chakrabarti et al, 1979). Similar findings have been documented by Johansen and Wiese (1970) and Tagaski et al (1979). Serum levels produced by different brands of phenytoin were compared in a bioavailability study where amorphous and crystalline phenytoin of particle size 17.5 - 45μm were used (Tammisto et al, 1976). The workers concluded that though there were differences in serum levels produced, there was no correlation between particle size and serum phenytoin levels. These findings may

however be criticised on the grounds that other factors such as excipients present may overshadow the influence of particle size.

Chakrabarti et al (1977) noted that a sharp improvement in dissolution rates occurred on the reduction of particle size below 125μm, but others have found that 74-149μm was a critical particle size and that further reduction had no influence on dissolution rates (Yakou et al, 1984). These differences are interesting since both groups of workers used powder formulations but it is likely that the differences are the result of the experimental conditions. Chakrabarti and co-workers used a propeller rotating at about 600 r.p.m. whilst the Yakou team used a paddle rotational speed of 100 r.p.m. Under the lower hydrodynamic agitation conditions, the aggregation of powders occurring in the particle size fraction of less than 50μm might well be pronounced and therefore particle size reduction may not show as an increase in effective surface area. Aggregation of micronised drugs is usually a problem and may be reduced when surface active agents are added to improve liquid penetration and dispersion. Also, by spreading fine drugs over coarse carrier particles using friction or by solvent deposition, the drug may be held in a deagglomerated state leading to a larger exposed surface area and consequently an increased dissolution rate.

1.2.3.3 Chemical Form

In preformulation studies, the problem of poor solubility may be counteracted by preparation of chemical forms with higher solubility. This is usually easily achieved by the preparation of salt forms of the drug.

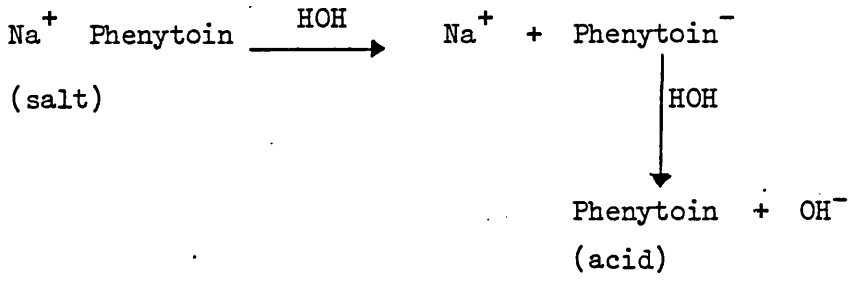
Salt formation of phenytoin takes place with the involvement of the imidic hydrogen through the occurrence of lactam - lactim tautomerism. These salts are readily soluble and the sodium salt is reported to have a solubility of 1g in 66 ml of water (Merck Index, 1984). The calcium salt has a slightly lower solubility (Ishiguro and Mogi, 1959).

Albani et al (1981) in their studies with two phenytoin preparations containing the acid and sodium salt, found that the formulation containing the salt form showed a higher in-vitro rate of dissolution. However, no significant difference in bioavailabilities between the salt and acid was found when they were both given to healthy and epileptic patients. Others have found that the sodium salt was more completely absorbed than the acid form (Lund, 1974b; Albert et al, 1974). Lund's results have been criticised by Tammisto et al (1976) who found that the acid formulation used had a particularly poor bioavailability. On the other hand, Stewart et al (1977) noted that by changing from Phenytoin Sodium BP to chewable acid tablet preparations a significant increase in plasma levels matched by a decrease in the number of seizures was noted. Similar results have been reported by others (Dill, 1956; Tammisto et al, 1976; Brandau and Wehnert, 1979).

At a fixed pH a drug such as phenytoin will have a fixed equilibrium solubility irrespective of whether the free acid or its salt is used. The dissolution rate on the other hand, may be higher for the salts of the weak acid than for the acid form itself. This is explained by consideration of the diffusion layer pH. The pH of the diffusion layer formed around the dissolving salt particles is greater than the bulk pH due to the contribution of hydroxyl ions, therefore, the effective localised solubility and dissolution rate is

increased. The equilibrium set up for phenytoin in water is shown below (Fig. 1.5).

Fig. 1.5 Equilibrium set up with phenytoin sodium in water



For phenytoin sodium one will expect the dissolved drug to precipitate as fine particles of phenytoin acid in the g.i.t. lumen, and these can easily be redissolved once absorption of drug from solution causes a fall below saturation. The fact that preparations of phenytoin acid may give comparable bioavailabilities to the salt would indicate that other formulation factors such as excipients, and drug particle size have to be taken into consideration. A well formulated acid product should therefore be able to give comparable or even higher bioavailability than the sodium salt (Dill et al, 1956; Glazko and Chang, 1972).

The question of the bioavailability of the calcium salt should theoretically follow a similar argument; however, the literature presents a similar seemingly confusing picture as for the sodium salt. Some researchers (Rambeck et al, 1977; Brandau and Wehnert, 1979) have reported higher bioavailabilities for the acid than for the calcium salt. In Germany, phenytoin was marketed as the calcium salt in Phenhydan tablets until 1976, when the formulation was changed for technical reasons to the acid preparation. Studies on this new

preparation showed that significantly higher serum levels were obtained than for the calcium salt. Medical personnel were then cautioned to monitor patients closely when there was a change in formulation (Rambeck et al, 1977). In Austria, in a comparative bioavailability study of several phenytoin preparations on the market, the authors found by considering the AUC, that the rates were in the order Phenhydan (calcium salt) > Epilan (phenytoin acid) > Epanutin (phenytoin sodium) >> Difhydan (phenytoin) (Nitsche et al, 1984). Obviously, in all these preparations other formulation factors appear to have a predominant influence. If the different salts and acid form were formulated using identical particle size in an identical dosage form, one would expect that dissolution and bioavailability would follow the order determined by the solubility Phenytoin Sodium > Phenytoin Calcium >> Phenytoin.

Another method of circumventing the poor solubility of drugs is the use of water soluble "pro drugs" which can convert to the active drug in the body. A common method is to prepare derivatives which may either contain an ionic, ionizable group or a chemical group which decreases the melting point (Amidon, 1981). The high melting point of phenytoin is attributed to the strong inter-molecular bonding in the crystal lattice between the hydrogen atom on the N(4) (see Fig. 1.1.a) and the carbonyl oxygen of a neighbouring phenytoin molecule (Camerman and Camerman, 1971). By disrupting this bonding in a bioreversible fashion and increasing the solubility of the drug, the compound may be formulated into a suitable dosage form. Yamoaka and co-workers (1983) have synthesised a homologous series of 3-acyloxymethyl derivatives of phenytoin and shown that superior bioavailabilities may be obtained if the 3-pentanoyloxymethyl derivative

was administered in tributyrin than for phenytoin. Bundgaard and Johnsen (1980) have also achieved enhanced dissolution rates by derivatisation of phenytoin through N-aminoethylation. Another method which has been used, is the preparation of the diethylaminoester of diphenylhydantoic acid. The sulphate salt of this compound undergoes ring closure under acidic conditions to form phenytoin and is about 9,000 to 15,000 times more soluble in water than phenytoin (Stella et al, 1975).

The prodrug approach is useful and has been used successfully in other applications; for example, the tranquillizer clorazepate is a prodrug of nordiazepam, an active metabolite of diazepam, and is marketed as the dipotassium salt (Gibaldi, 1984). In the case of phenytoin, the preparation of prodrugs seems to be mainly of theoretical interest since other simpler methods of improving the bioavailability exist without the need to resort to prodrugs.

1.2.3.4 Excipients

McQueen (1968) and Tyrer et al (1970) have described the outbreak of anticonvulsant intoxication in Australia, in 1968, when patients stabilised on a formulation of phenytoin sodium containing calcium sulphate dihydrate was changed to one containing lactose. It was proposed that phenytoin was less bio-available when formulated with calcium sulphate and it has been suggested that an insoluble complex of the drug was formed during dissolution, as higher levels of the drug were excreted for lactose formulations (Bochner et al, 1972b; 1973). Bastami and Groves (1978) also studied the effect of excipients including calcium and magnesium salts on the in-vitro release. The drug was not released when magnesium sulphate was used

as excipient; these authors have also suggested that insoluble magnesium complexes may have been formed. Most other workers have found no evidence of interaction between phenytoin sodium and calcium sulphate (Chapron et al, 1979; Dunn, 1982; Rubino et al, 1985). The question of reduced bioavailability in the presence of calcium sulphate is linked also with the effect of concurrent administration of antacids (O'Brien et al, 1978; Chapron et al, 1979) or calcium rich foods (Herishanu et al, 1976) on the bioavailabilities of phenytoin. Results of these studies are conflicting but it has been suggested that the reduced absorption may be due to a direct effect of calcium ions on the intestinal membrane.

The presence of excipients may be used to enhance the dissolution of poorly soluble drugs. Various methods are available and some have been successfully employed for phenytoin. Sanghavi and Kamath (1984) incorporated the surfactant polysorbate 80 or sodium lauryl sulphate into the phenytoin mass and noted improved dissolution as compared to the drug alone. Chakrabarti, Belpaire and Moerman (1980) also observed high dissolution rates for Phenytoin tablets containing phenytoin precipitated with polysorbate 80 which were comparable to those of the sodium salt. Surfactants improve dissolution by lowering the interfacial tension between the dissolution medium and the drug particles thereby aiding penetration, wetting and subsequently dissolution.

Other methods which have been applied to enhance dissolution include the formation of solid dispersions using a suitable carrier. Common carriers which are normally used are the polymers polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP). These dispersions may be prepared either by melt/fusion or by the use of co-solvents.

Normally the ratio of drug to polymer is low to maximise the increase in dissolution. Solid dispersions of phenytoin with PVP have been prepared and shown to improve dissolution rates and bioavailability (Sekikawa et al, 1978; Nozawa et al, 1985). PVP is a non-crystalline polymer and by preparation of solid dispersion, the drug is transferred to a high energy or amorphous form which is easily dissolved. A reduction in the molecular weight of the PVP used improves the solution rates probably as a result of the reduction in viscosity around the dissolving drug particles. Yakou et al (1984) and Stavachanski and Gowan (1984) obtained improved dissolution and bioavailability using PEG 4,000 and PEG 6,000 respectively. Data for phenytoin formulated as a solid dispersion with PEG 6,000 show it to be bioequivalent to prompt phenytoin sodium capsules. PEG unlike PVP, is highly crystalline and is thought to be capable of trapping low molecular weight drugs in the interstitial pores.

Other polymeric carriers recently evaluated are the natural cyclodextrins (-CyD). These are non-crystalline and the β-cyclodextrin has been shown to improve dissolution of the drug (Tsuruoka et al, 1981); Hegde and Rhodes, 1985). They contain interstitial spaces which are capable of trapping molecules. The cavity sizes are 5.2Å , 6.4Å and 8.3Å for the larger entrance sides of the α , β and γ-CyD's respectively. The cavity size of β-CyD seems to be optimum to entrap the phenytoin molecule and consequently provides the greatest solubilization effect. The drug has been found to be present in the amorphous form and there seems to be hydrogen bonding between the phenytoin and the cyclodextrin suggesting complex formation. However, because of the limited solubility of the β-CyD's, its usefulness is limited. Condensed polymers of CyD's with epichlorohydrin, (CyD's-EP),

have also been used. The rapidly dissolving β-CyD.EP complex was found to significantly increase plasma levels of the drug after oral administration to dogs (Uekama et al, 1985). Yakou et al (1986) have reported enhanced dissolution rates by co-precipitating phenytoin with the bile acid, sodium deoxycholate (DC-Na). They have also evaluated the dissolution characteristics and bioavailability of phenytoin prepared with various combinations of DC-Na and water soluble polymer carriers. The combinations used were DC-Na with PVP, DC-Na with PEG and DC-Na with hydroxypropylcellulose. All the co-precipitates prepared enhanced the dissolution rate but the PVP-DC-Na (1:1) showed the fastest release rate.

Solid surface dispersions of a drug on suitable carriers can also alter its dissolution characteristics. This can be achieved by deposition of the drug on the solid carrier from solvents or by grinding with certain materials. Improved dissolution is a result of the drug being deposited in a micronised state on the carrier, thus improving the wettability and effective surface area of the drug. The use of the insoluble carrier, silicon dioxide, has been described by Guernten and Jaminet (1978). Johansen and Moeller (1977) deposited 2% phenytoin on lactose or silicon dioxide by first dissolving the drug in ethanol. The dissolution rate was initially slower from the lactose system but, unlike silicon dioxide, continued to completion. With silicon dioxide the release did not exceed 91% of theoretical concentration, due to adsorption of the drug on the surface of the carrier.

Lerk et al (1979) have hydrophilised the drug by grinding with methylcellulose. Bioavailability studies showed rapid absorption for the treated drug in contrast to a one hour absorption lag time for the

untreated drug. By intense grinding of phenytoin with micro-crystalline cellulose, Yamamoto and co-workers (1976) have converted the crystalline drug into the amorphous state with subsequent improved in-vitro and in-vivo performance. Crystalline cellulose, chitin and chitosan have also been used as carriers for phenytoin. The release rates from a ground mixture with chitosan showed fastest dissolution followed by that with chitin and the least with crystalline cellulose (Sawayanagi, Nambu and Nagai, 1983). Enhancement of the dissolution rate of phenytoin has also been achieved by grinding with gelatin (Kigasawa et al, 1981).

Rosen and Macheras (1984) have used the proteins Human Serum Albumin (HSA) or casein to obtain an improvement in both the rate and extent of dissolution. It was shown that at pH 4 the presence of protein increased the solubility and also dissolution of drug. This is achieved by the binding of phenytoin to protein in the diffusion layer thereby solubilising the drug at levels higher than those achieved in the bulk medium. Enhanced transfer across the diffusion layer as a result of the increased concentration gradient also influences the dissolution rate observed. A study of the effect of protein in everted gut preparations showed that protein binding in the mucosal solution causes a decrease in apparent transfer rate and may account partially for the influence of food on phenytoin bioavailability (Rosen and Macheras, 1985).

From the literature, the presence of excipients appears to modify most significantly the dissolution rate of phenytoin. Similar conclusions have been obtained from experiments by Yakou et al (1981).

1.2.3.5 Manufacturing conditions

Apart from factors such as drug particle size and the use of excipients, the method of preparing the powders in a solid dosage form can influence the drug dissolution characteristics.

Yakou et al (1982) have considered the influence of manufacturing conditions on the dissolution and bioavailability of phenytoin. The powders considered were commercial phenytoin crystals, freeze-dried crystals, powders prepared by simple blending with excipients or by solvent deposition of the drug on excipients. Freeze-dried powders showed higher dissolution rate than the original commercial form of the drug when dissolution testing was performed in artificial gastric fluid. A 20% powder preparation of phenytoin prepared by solvent deposition produced saturated concentrations of phenytoin in 20 minutes as compared to more than two hours for the commercial powders. The rate was also higher than for powders prepared by simple blending.

Kohda et al (1983a) compared phenytoin products prepared by alternative wet granulation processes and found little difference between freeze-dried fine granules and ordinary fine granules. They concluded that manufacturing conditions involving granulation could be interchanged without causing toxicity in patients. Simple mixtures of drug with excipients gave slightly lower absorption. This is because granulation provides improved contact of drug with excipients, similar to that produced during preparation of dispersions using co-solvents. Nozawa, Mizumoto, Higashide (1985) compared dissolution rates of phenytoin prepared either by roll mixing with PVP, co-precipitation or simple physical mixing. The dissolution rates of the roll-mixed form were superior to those of physical mixes and the

co-precipitates at any PVP concentration from 25% to 85%. During roll-mixing, the intense grinding conditions progressively breaks the inter-molecular covalent bonds until the rigid crystalline structure is destroyed and an amorphous material is produced. The authors found that mix grinding procedures were time consuming for products with high drug content and in co-precipitation it was difficult to completely remove the residual solvent which could adversely influence dissolution. On the other hand roll-mixing was rapid, simple and efficient.

1.2.3.6 Dosage forms

Phenytoin is usually formulated as a suspension, capsule or tablet. The oral solution is not normally used as it is known to cause nausea, vomiting and diarrhoea. Miles, Attwood and Seddon (1976) found the suspension the most efficacious preparation followed by capsules and tablet; however blood level obtained with the suspension was difficult to maintain. In another study of 9 products available on the Canadian market, the extemporaneous suspension showed a high between-study variation (Sved et al, 1979).

Neuvonen, Pentikainen and Elfving (1977) also observed that the suspension normally gave higher dissolution rates than tablets but found that the particle size of the drug in the suspension was important. A well formulated tablet may give a higher dissolution profile than a suspension if the particle size of the latter was too large. They further cautioned other researchers on the practice of using suspensions as reference material. In another study, the AUC, C_{max} were found to be significantly lower for rapid release capsules and for solutions than for slow release capsules but the incidences of toxicity and nystagmus did not differ much. One would

think that this was because the dosage regime used was not towards the upper limit of the therapeutic range. The oral solution showed more frequent mental related side effects though the authors suggested that this could be a result of the solvent systems used (Sawchuck et al, 1982).

Smith and Kinkel (1976) have reported no difference in bioavailability between tablets and capsules although others have noted much lower blood levels with tablets than for capsules. Recently, in the U.S.A., phenytoin toxicity was noted in a patient when tablets were substituted for capsules (Kirshner, 1983). Manson et al (1975) also found similar results but suggested that the difference was a result of the tablets being ingested without being chewed. Bielman and Levac (1978) found no difference in bioavailability whether the tablets were chewed or not. They reformulated the tablet product by converting it into a capsule formulation and noted higher dissolution rates, but in their capsule dosage form, the crushed tablets were mixed with lactose and talc before encapsulation. Two variables have been introduced and it is difficult to differentiate the effect of encapsulation from added excipients. Bastami and Groves (1978) obtained higher dissolution profiles for tablets compressed from commercial capsule contents than from capsules prepared from ground sugar-coated tablets. A log probability plot indicated that tableted capsules had a simple unimodal pattern whilst capsules made from tablets were bimodal. This strongly suggested that the characteristic bimodal behaviour of the capsules was due to the capsule shell. Absorption of phenytoin from powder was low, variable and decreased with increasing dose as compared to tablet formulations (Kohda et al, 1983b).

The interpretation of evidence obtained from the available literature is slightly confusing as, in most reports, little effort is taken to standardise other formulation factors such as particle size and excipients. It would nevertheless seem reasonable to conclude that the dissolution rates and availability of the drug will be least for coated tablets and then increase for compressed tablets, powder filled two piece hard capsules and suspensions with best bioavailability being shown by solutions.

1.2.3.7 Relative Humidity and ageing

Levy and co-workers (1963) have pointed out that drug release studies performed just after the preparation of a formulation are not of much significance since release patterns can change on storage. This can lead to significant differences in the biological availability of a drug compound especially in formulations where dissolution is the rate-limiting step in absorption.

Akbuga et al (1984a) have studied the effect of ageing and Relative Humidity (RH) on various commercial tablets and capsules of phenytoin sodium and found that the release rates differed from lot to lot after storage. The lots with higher release rates before storage generally decreased on storage and those with lower rates initially, had improved rates after storage. In a continuing study, on experimental phenytoin sodium capsules containing lactose as diluent, capsules were stored at 75% or 95% RH for 8 weeks. They found that generally there was a reduction in in-vitro release after storage at 95% RH (. AKbuga et al, 1984b). A similar study was conducted in America where the influence of formulation and storage on in-vitro release of phenytoin sodium capsules was studied after storage at 11% and 67% Relative Humidity. The authors found several interacting effects between storage conditions and formulation factors.

Capsules containing lactose generally showed a retardation of release on storage but those containing calcium sulphate improved (Rubino et al, 1985).

Neither of these workers explained the causes of their observations though phenytoin sodium is known to be hygroscopic and also unstable in the presence of carbon dioxide (Merck Index). Gupta and Gupta (1979) studied the stability of some oral drug products when stored with or without silica gel in a counting machine and also in an original container. Phenytoin sodium capsules stored in the machine were stable but absorbed more moisture than those in the original container (6.8% as against 0.3% weight gain). Silica gel, surprisingly, did not reduce the amount of moisture absorbed by the capsules. The dissolution and disintegration times were affected by storage in the counting machine but no mention was made of whether the rates were increased or decreased.

Phenytoin sodium forms higher hydrates, the mono-,tetra-, hepta-, octa- and hendecahydrates are formed under high relative humidities. The tetra- and hepta- forms appeared to be most stable under conditions of high humidity with a moisture content of 20.8 and 31.5% respectively (Ishiguro, Kozatani and Shibata, 1958). Also, the absorption of carbon dioxide by phenytoin sodium increased with the degree of hydration forming sodium bicarbonate and phenytoin (Ishiguro et al, 1955). Obviously, the influence of storage and humidity on the dissolution of phenytoin sodium capsules will depend on the stability of the drug and excipients and the interactive effect of the two. Oppenheim and Hersey (1977) in an excellent review have commented on the physical and chemical changes of powders on storage.

1.3 POWDER MIXING

Solid-solid mixing of dry powders is a preliminary step in the preparation of solid dosage forms. The objective of powder mixing is to prepare a mix where the spatial configuration of the various particles determines the property of the final dosage form. More commonly it is undertaken to obtain mutual distribution of constituent ingredients such that each unit dose provides the patient with the same quantity of active ingredient.

The mixing processes of particulate systems differ from those in liquid or gas systems in three main respects. Solids form a mechanical network as a result of inter-particulate forces and do not have intrinsic mobility like gases or liquids. Therefore energy must be imparted to attain particulate motion. Also, particles have sizes several orders of magnitude larger than the molecular sizes of liquids or gases and as a result the level of homogeneity attainable is limited. Finally, particulate solids do not have the constant properties of molecular species and can differ widely in their physical characteristics. Therefore, a mixing mechanism which depends on identical physical properties is unlikely to achieve its ideal objective.

When energy is imparted to a powder bed containing two powders to be mixed, the powder bed expands or dilates to accommodate particle movement. In general the more dilated a powder bed the more easily relative particle motion can occur. Ideally the motion of particles within a mixer must be random, three-dimensional and there should be no movement of groups within which no relative motion occurs. In practice, mixing of solids occurs by a variety of mechanisms: shear, convective or diffusive mixing. In any given apparatus one or more of these may predominate. Convective mixing occurs by the distribution of particles over freshly exposed surfaces, diffusive by

the transfer of groups of adjacent particles from one location to another and shear mixing when slip planes are formed within the powder mass, causing bulk rearrangement of different sections.

1.3.1 Mixing theories

Two main theories have been proposed to explain scientifically the formation of powder mixes: those formed by randomisation and those formed by mechanisms other than randomisation. In the second category are those mixes formed by ordering and other non-random mechanisms. In practice these two divisions are not so clear cut and there exist between the two extremes, mixes which owe their homogeneity to a combination of the two. These include partially-ordered random mixes and total mixes (Staniforth, 1980). The final structure of a powder mix is influenced largely by the extent of interaction between the particles. This interaction may in turn be affected by physical properties such as particle size, size distribution, density, bulk density, shape, surface roughness, agglomeration tendencies, flow characteristics, moisture and lattice defects.

Staniforth (1982a) has presented a review on the processing of pharmaceutical powders containing 132 references, with emphasis on the theories of powder mixing and powder segregation.

1.3.1.1 Random mixing theory

Random mixing of powders has been described as that operation in which motion is imparted to particles to cause them to assume arrangements such that as mixing proceeds, the frequency distribution of sample compositions becomes increasingly narrow and approaches the binomial distribution at equilibrium (Weidenbaum and Bonilla, 1955). The individual powder components start from a system of order and

mixing continues until a state of randomness is reached where the probability of finding a particle of any component is the same for all points in the mixture. The degree of mixedness within the mix can be described by any statistical parameter which takes into account the spread in distribution of samples taken. Normally, an inverse function of the variance or the standard deviation is used.

Lacey (1943) derived an equation for a completely random binary mix consisting of particles distinguishable from each other by colour only, e.g. black and white particles. See Fig. 1.6.

$$\sigma^2_R = x.y/n \qquad \text{Equation 1.8}$$

where σ^2_R, is the variance of the random mix; x and y, the proportions of component powders and n, the total number of particles in each sample. In actual practice, particulate systems rarely have identical physical properties and the equation was extended to account for differences in size, shape and density of component particles (Stange, 1954).

$$\sigma^2_R = x.y/\frac{M}{[y(\bar{w}(1+\bar{s}^2/\bar{w}^2))_x + x(\bar{w}(1+\bar{s}^2/\bar{w}^2))_y]} \qquad \text{Equation 1.9}$$

where M, is the mass of the sample taken from a mix; $\bar{s}(\bar{s}_x, \bar{s}_y)$, the standard deviation of the particle weights of the mix components and $\bar{w}(\bar{W}_x, \bar{W}_y)$, the mean particle weight of each ingredient. Later Stange (1963) extended his equation to account for multi-component mixtures. To calculate $\bar{w}$, $\bar{s}$, the respective size distribution of each powder must be known. Poole et al (1964) simplified the equation to:

$$\sigma^2_R = x.y/\frac{M}{y(\Sigma fw)_x + x(\Sigma fw)_y} . \qquad \text{Equation 1.10}$$

where $\bar{w}$, is the weight of each size fraction, f.

Train (1960) first applied Equation 1.9 to pharmaceutical mixtures. He pointed to the difficulties encountered with mixtures containing small quantities of active ingredient and at the same time emphasised the importance of controlling particle size in obtaining a homogeneous mixture. Johnson (1972) showed that the modified equation of Poole et al could be simplified for mixes containing less than 1% of drug without loss of accuracy.

where $x \ll y$

and $x + y = 1$, $x(\Sigma fw)y \ll y(\Sigma fw)x$

then $\sigma^2_R = x/M\,(\Sigma fw)_x$ Equation 1.11

Where the drug content was between 1 and 10% the equation approximates to:

$$\sigma^2_R = \frac{x.y^2}{M} \cdot (\Sigma fw)_x \qquad \text{Equation 1.12}$$

Independently Buslik (1950) derived an equation for the variance of a multi-sized mixture.

$$\sigma^2_R = \frac{P_a\,(1-P_a)\bar{W}_a}{M} + \frac{P_a\,(\bar{W}-\bar{W}_a)}{M} \qquad \text{Equation 1.13}$$

where $\bar{W}_a$ is the average particle weight of a single size fraction of proportion P_a, $\bar{W}$, the average particle weight of the whole mixture

where $\bar{W} = P_aW_a + P_bW_b + \ldots\ldots\ldots\ldots$ Equation 1.14

Harnby (1967) compared the Equations 1.9 and 1.13 of Stange and Buslik and found them to be identical. The first term in Equation 1.13 is equivalent to Lacey's equation when all the particles have a constant mass and the second term is the variance increase due to the

variable size of the second component. This variance would be decreased by keeping the size of one component small and also by keeping the particle size of the second component as close as possible to that of the first ingredient.

Kristensen (1973) developed an equation by assuming that the samples contained a constant volume of solid. Where the particle density of the two components were equal, the equation was identical to that of Poole, Taylor and Wall (1964).

$$\sigma^2_R = \frac{x.y.}{M} \frac{\rho^4}{\rho^2_x \rho^2_y} \cdot [x\bar{w}_y . y\bar{w}_x] \qquad \text{Equation 1.15}$$

where ρ, is the mean particle density of the mixture of components x and y.

In practice where σ_R is small representing less than 2% of the mean, the standard deviations due to the sampling, σ_S, analytical procedures, σ_A, and purity of sample, σ_P, cannot be ignored. Thus the lowest standard deviation σ_E, that can be achieved for even the idealised system of Lacey (1943) would be:

$$\sigma_E = \sigma_R + \sigma_A + \sigma_S + \sigma_P. \qquad \text{Equation 1.16}$$

1.3.1.2 Non-random mixing theory

The random theory of mixing describes a theoretical powder mix where the physical properties of the components allow for complete random mixing. In actual practice this final equilibrium state is never reached due to incomplete mixing and segregation. Williams (1970) called this process non-random. The final structure of such a powder mix has an overall uniformity but not of individual particles as described by Lacey and is represented by Fig. 1.7. The probability,

P_x, of finding a particle of a given component, x, at any point in such a mixture is a function of the position at which the sample is taken. The variance σ^2_{NR} is given by:

$$\sigma^2_{NR} = \int_0^1 [(\bar{P}-P_x)^2 + P_{x/n}(1-P_x)]\,dx \qquad \text{Equation 1.17}$$

and dx, relates to the position of the sample from a reference point. When the probability is constant as in a random mixture, and is equal to the proportion of one ingredient, the equation derived is equivalent to Lacey's:

$$\sigma^2_{NR} = \frac{P(1-P)}{n} \qquad \text{Equation 1.18}$$

Kristensen (1973) used the correlation coefficient, r, to describe the state of mixedness where r is one when the system is unmixed and zero when a completely random state is reached. In a non-random mixture the variance is given by:

$$\sigma^2_{NR} = r.\sigma^2_o + \frac{\sigma^2_o + r\sigma^2_o}{n_e} \qquad \text{Equation 1.19}$$

where σ^2_o, is the variance of an unmixed mixture and n_e, the effective particle number in the sample of mean weight W, and effective particle weight, W_e, given by:

$$n_e = W/W_e \qquad \text{Equation 1.20}$$

In the two types of theories described, random and non-random, the mixtures formed do not interact physically with each other and the mixture is made up of individual particle units.

Fig. 1.6 Ideal random mixture of equal proportions of black and white particles

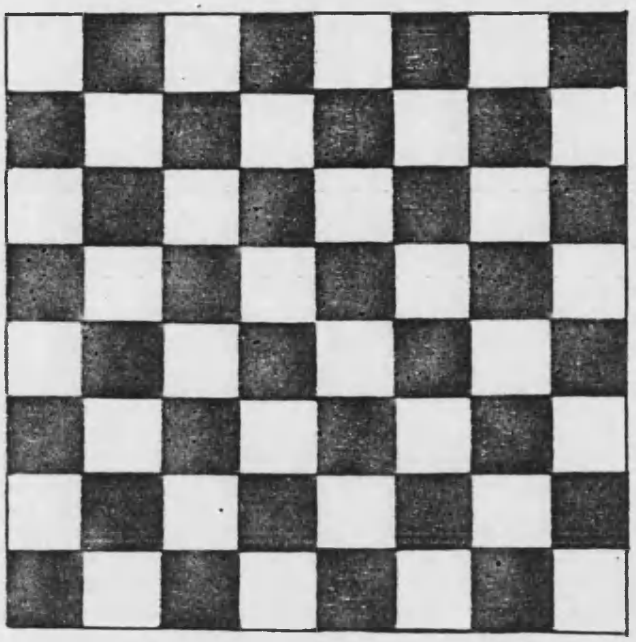
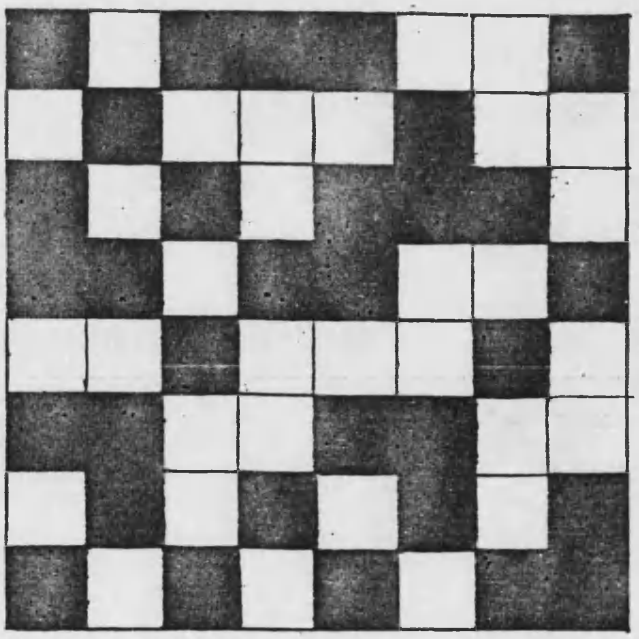


Fig. 1.7 Randomised mixture of equal proportions of black and white particles

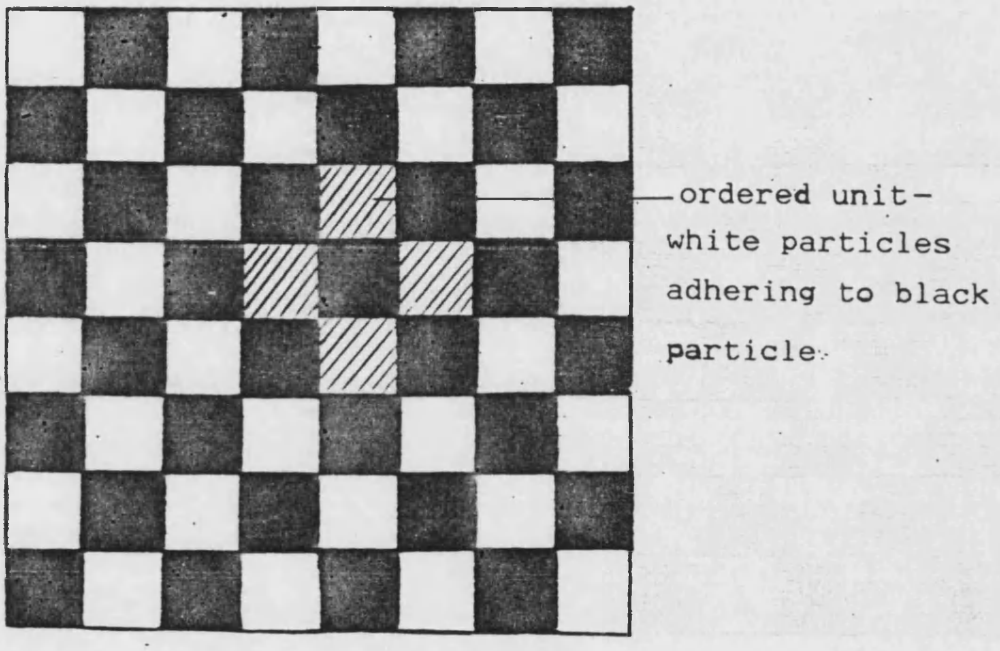


1.3.1.3 Ordered mixing

Until recently the only acceptable theory of powder mixing was based on the statistical randomisation of non-cohesive powders as described by Lacey. However, it had been recognised in the literature that one set of particles, usually fines, may adhere on another set influencing both the mixing behaviour (Travers and White, 1971) and flow of the powders (Jones and Pilpel, 1965). Hersey (1975) first introduced the concept of order in mixing to explain logically the mixing of small cohesive particles to obtain a considerable degree of homogeneity. He represented the ordering diagramatically as shown in Fig. 1.8, but pointed out that ordered mixtures were more likely to occur where there were fewer "black" particles and many small "white" particles. He explained that particles less than 100μm in diameter had surface forces outweighing gravitational and inertial forces which determined the particle movement. As such, these particles were cohesive and mixing of fines with coarse particles would lead to segregation unless other interacting forces were present to homogenise the mix. In ordered mixing, particles inter-act through any form of adhesion forming ordered units. The ordered unit is defined as the smallest part of the mixture that constitutes the ordered mix (Hersey, 1977). Hersey (1977) also recognised that ordered units may be formed mechanically or by coating of fines on a carrier during solvent deposition.

The high degree of homogeneity obtained in ordered mixes is attributed to adhesion of fines to surface asperities, irregularities and also to lattice defects (Hersey, 1980). Specific examples of these have been reported in the literature (Crooks and Ho, 1976; Huttenrauch and Keiner, 1979; Staniforth, 1980). Assuming that

Fig. 1.8 Ordered mixture of equal proportions of black and white particles



particles are spherical, it is possible to calculate stereometrically the number of fines which can adhere to the surface of a coarse carrier particle as a monolayer. This number is only of theoretical interest as not all the sites on a particle are binding sites and suitable for adherence. The equation may be given as:

$$N^{\circ} = \frac{2\pi(D+d)^2.f}{\sqrt{3}d^2} \qquad \text{Equation 1.21}$$

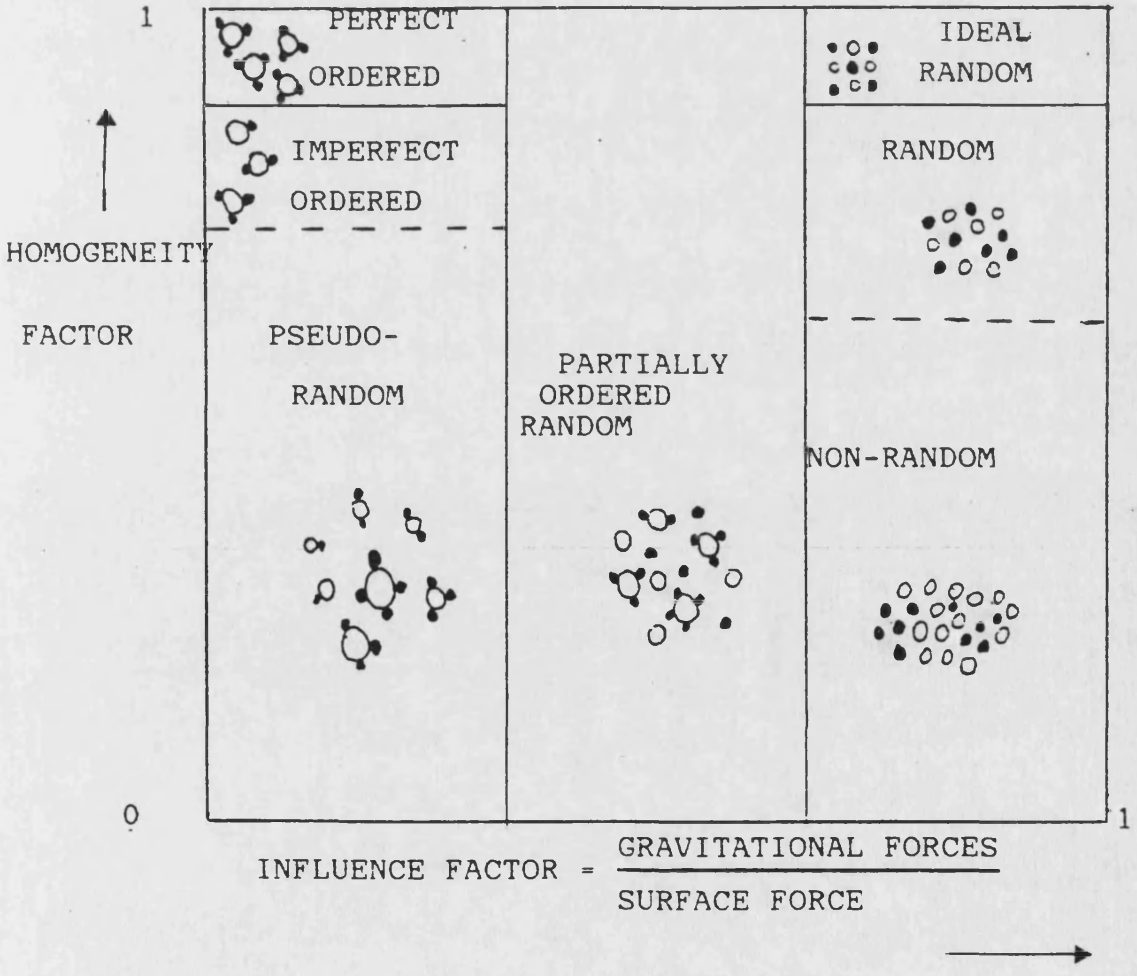
when N°, is the number of binding sites; D, the coarse carrier diameter; d, the fine particle diameter and f , the fraction of the surface covered by fines. From the equation the number of binding sites may be increased by increasing the ratio of D to d that is, by an increase in carrier size and decrease in fine particle size.

1.3.1.4 Total mixing

Ordered mixes are formed when particles interact unlike in random mixes, where these forces are non-existent. In practice, it is not possible to carry mixing to the ideal state in which there is an identical number of fines on all coarse carriers, though it has been recognised that the problem of segregation may be overcome by classifying particle sizes to narrow limits (Yip and Hersey, 1977a). As most carriers used will have unequal sized particles, pseudo-random mixes may be formed where an unequal number of fines adhere on the carrier surfaces (Egermann, 1980). Hersey, Thiel and Yeung (1979) have also described the partially-ordered randomised situation where there were agglomerates of one set of particles mixed randomly with pseudo-random units.

Staniforth (1980) recognised that the two types of mixes, ordered and random, existed at two opposite ends of the scale but that real mixes contained any combinations of the two mixing

Fig. 1.9 Schematic representation of total mixes based on relative influences of gravitational and surface forces in a given set of particles and on the homogeneity of the mix. (Staniforth, 1982b)



mechanisms and described such a mix as a total mix. This would include the pseudo-random mixes and partially ordered random mixes described above. The domination of a particular spatial arrangement in a powder structure could be predicted by the relative influence of surface and electrical forces (Fig. 1.9). Where surface forces predominate, ordering mechanisms may occur whilst random mechanisms would be formed when gravitational forces predominate. The extent to which randomisation or ordering may occur would also depend on the conditions of the mixing operation. Thus the total structure of a real pharmaceutical mix would contain all the types of mixes described and this would determine the homogeneity within the mix.

1.3.2 Interparticle bonding forces

The types of forces which may exist between two particles have been identified as: London-van der Waals, electrostatic, magnetic, chemical, mechanical forces and solid bridges. These forces do not normally work alone but usually a combination of forces exists. Also most particles will have moisture present on their surfaces, under normal environmental conditions, which will modify further the forces already present. Some of these forces have been quantified in certain cases.

Ordered mixing in the pharmaceutical industry requires particle-particle interactions through adhesive forces and, therefore, it is unlikely that all of these forces occur. As pointed out by Krupp (1967), the surfaces of most particles are ordinarily chemically saturated so that chemical bond formation across the interface is highly improbable. Certain powders may show magnetic properties and strong attractions, which decay slowly, can exist between such particles. Pharmaceutical powders are, however, basically diamagnetic and magnetic forces would not be likely to lead to ordering within the powder mix.

Mechanical forces arise as a result of friction and interlocking of projections on particle surfaces; when mixing fines and coarse carriers, asperities and cavities on the carrier surface may act as sites to lock fine particles in position. By themselves mechanical forces do not cause interparticulate bonding but react to particle movement. Staniforth (1980) has prepared highly macroporous lactose and shown that these particles, as well as Emdex particles, formed stable mixes which did not segregate at high accelerations and low frequencies. Mechanical interactions are therefore most useful when the stability of a powder mix is under investigation.

Another type of bridging that can occur between particles is solid bridging. They may occur during crystallization, sintering or asperity melting, dissolution and alloying. In the pharmaceutical field solid bridges or mechanical links may occur during the storage or drying of powders, when crystalline bridges may form. Also crushing and bonding of solid particles may occur due to brittle fracture and plastic deformation in dry compaction processes. During wet granulation, mechanical links are also formed between powder particles. However, it is unlikely that mechanical links may lead to ordering during powder mixing. As a result, the main forces of interest in pharmaceutical ordered mixing are:-

1. London-van der Waals forces
2. Electrostatic forces
3. Moisture bonding

1.3.2.1 London - van der Waals forces

The forces between two solids due to dispersion or London - van der Waals forces arise from the electric motion of atoms on the

surface and from atoms in the interior of the solid. They may be explained as follows, an atom, has because of the motion of electrons an instantaneous dipole moment, the time average of which is zero. These dipoles generate an electrical field which induces in a neighbouring atom a dipole moment. The interaction between two dipoles gives rise to an instantaneous attractive force between two neutral atoms whose time average is finite.

There are two approaches for calculating the dispersion force between two solid surfaces. The first, the microscopic approach was used by Hamaker (1937) who added the interactions between all pairs of atoms to calculate the van der Waals potential for a solid body. This approach has been modified by Clayfield et al (1971) to take into account the "retardation effect" noted when particles are separated by distances greater than 50nm. Although Hamaker's treatment is of great value, the approach has three main defects (Tabor, 1982). A more satisfactory method has been used by Lifschitz who treated each body as a continuum and expressed the interaction in terms of the dielectic properties of the two bodies. This method is known as the continuum or macroscopic approach and is particularly useful when bodies are separated by a medium other than air.

Both approaches are misleading when the separations are less than 0.2nm and in particular in cases of atomic contact where interactive energies may be of the order of about twice the calculated dispersive energy (Tabor, 1982). However, depending on the geometric model used, i.e. plane/plane, sphere/plane or sphere/sphere, and the theoretical approach taken, different relationships exist for the approximation of adhesion by London-van der Waals forces. These have been critically compared by Krupp (1967).

Basically, all the equations differ mainly in the constants generated but the adhesive force, F_v , is always proportional to the particle diameter, d and inversely proportional to the square of the distance, a. The equations may be simplified to:

$$F_v = k. \frac{d}{a^2} \qquad \text{Equation 1.22}$$

where k, is a constant inherent in the solid material (Shinohara, 1984).

London-van der Waals forces act over short distances of about 10^{-3}m. Addition of the force is required for multi-point contact and therefore surface roughness must be taken into account in non-ideal spheres or particles. They are weak forces but the effect increases as the particle size decreases and they are the major forces affecting the behaviour of particles less than 10μm. These forces have been measured for a number of particulate solids. In the pharmaceutical field, Staniforth et al (1981) have measured the adhesional force between ordered units of salicylic acid and other excipient carriers. They concluded that the van der Waals forces contributed mostly to the force of adhesion between the particles.

1.3.2.2 Electrostatic forces

Powder particles may acquire electric charge on their surface by ion-particle impact, particle-particle collision or fracture of particles where covalent and ionic bonds may be broken. The first two processes may be induced as in diffusion or field charging but more commonly they occur during contact charging. In operations such as transport of powders through pipes, storage and mixing

powders become electrically charged by contact where electrons are transferred when dissimilar materials touch each other. This has been thoroughly discussed by Harper (1967) and Bailey (1984). For pharmaceutical powders, which are basically insulators, particles have a high resistivity and there is no flow of electrons from bulk material. Therefore, the presence of impurities or dislocations act as a source of charge transfer. When charging occurs, the charge is redistributed over the surface of particles. For spheres, the final equilibrium charge density is uniform but for non-spherical particles a higher than average charge occurs in regions of higher than average curvatures. The charge is also believed to extend diffusely into the body for about 1μm. Also, the maximum field attainable depends on factors such as particle size and environmental conditions.

The existence of surface charge gives rise to an electrostatic field which decays inversely with the square of the distance from the surface and therefore contact is not essential for bonding, and electrostatic forces may be effective over macroscopic distances. A point charge will induce an identical but opposite force on another neutral body and the force, F_c, between these two point charges q_1, q_2 can be calculated from Coulombs Law. Where a number of charges are distributed uniformly or nearly uniformly on a particle surface, the electrostatic force experienced may be given by:

$$F_c = \frac{q_1 q_2}{4\pi E_o E_r a^2} \cdot \alpha \qquad \text{Equation 1.23}$$

where E_o, is the influence constant,

E_r, the dielectric constant,

α, the weighted effect from all the point charges and

a, the distance of separation of the point charges.

Identical charges on particles will produce repulsion whilst opposite charges produce attraction. In the equation given above, it is assumed that the particle diameter is small as compared to the distance of separation. For macroscopic bodies, the equation must be modified to account for particle geometry (Krupp, 1967).

Charged particles have altered powder flow properties due to sticking of powders to each other and to the surface of the substrate (Staniforth, 1981). Gold and Palermo (1965) recorded a negative charge for crystalline acetominophen flowing down a hopper which was reduced by the addition of excipients such as dicalcium phosphate dihydrate, mannitol, spray dried lactose and most significantly by 2% magnesium stearate and talc. They explained the effect in terms of the antistatic property of talc and magnesium stearate. It is interesting that the work of Staniforth and Rees (1982) also showed positive charges for magnesium stearate when contacted with glass or polyethylene surfaces. This positive charge is believed to form strong electrostatic bonds with negatively charged carriers, forming ordered units. It has been noticed (Staniforth and Rees, 1981; 1982) that ordered mixes formed between powders with like-charges are less stable than those containing opposite-charged particles. These authors have further optimised the observation by using tribo-electrification or contact charging with rubbing, to give optimum opposite charges on excipient and drug particles. The procedure facilitated ordered mixing and also improved the stability of the powder mix. The technique is particularly useful for the formation of ordered mixes with smooth-faced carrier excipients such as Dipac. Also, in cases where a porous carrier has become saturated, with fine particles at excess concentrations, electrostatic charging can be used to reduce segregation tendencies (Staniforth, 1985a).

1.3.2.3 Force due to presence of moisture

As a result of van der Waals forces, particles may adsorb molecules from the environment. Commonly water molecules are adsorbed and the volume adsorbed depends on the pressure, temperature, relative humidity of the environment and also the nature of the solid. Moisture may be present either as adsorbed vapour if the humidity is above a critical value, or as liquid bridges at higher humidities.

Coelho and Harnby (1978) have worked out the attractive force, f, experienced between two un-equal sized spheres due to adsorbed layer bonding using as unit force the weight of the smaller particle,

$$f = \frac{3 \times 10^5 (\delta - y/2)}{\gamma R_2^2} \cdot \frac{m}{m + 1} \qquad \text{Equation 1.24}$$

where δ, is the thickness of the adsorbed film on two spherical particles the distance of separation, y, measured in $\mathring{A}$; m, the ratio of the radii of the spherical particles R_1 and R_2, where R_2 is much larger than R_1; γ , the specific gravity of the liquid adsorbate in g/cm^3, m and f are dimensionless values. The bonding is caused by overlapping of the adsorbed layers of neighbouring particles and its strength is proportional to the contact area and strength of the film.

When a liquid bridge of low viscosity forms between two particles, a force, F_H, acts between the two solid components consisting of the surface tension force, F_R, and force, F_p, due to difference in pressure outside and inside the bridge.

$$F_H = F_R + F_p \qquad \text{Equation 1.25}$$

Whilst the surface tension force always leads to attraction the capillary pressure only contributes to attraction when a pressure deficiency exists within the bridge. For spheres of equal size, the force of adhesion due to a liquid bridge is given by:

$$F_H = \sigma_{lg} d\, f(\alpha, \theta, \frac{a}{d}) \qquad \text{Equation 1.26}$$

Where σ_{lg}, is the surface tension of the liquid/gas interface; d, particle diameters and $f(\alpha, \theta, \frac{a}{d})$ is a function of α, the bridge angle; θ, the contact angle and a, the distance of separation (Schubert, 1984). Depending on the geometry of the adjacent particles, for example spheres of different sizes, cones and spheres (which is supposed to represent a regular rough particle on the surface of sphere where the conical projection occurs at the point of contact) Equation 1.26 may be modified accordingly.

In a low humidity environment, electrostatic or van der Waals forces may dominate but at elevated humidities moisture bonding may predominate. Unlike electrostatic, van der Waals, magnetic or chemical forces, forces due to moisture bonding occur where there is already contact between particles brought about by other mechanisms. Coelho and Harnby (1978) have discussed further the variation of inter-particulate forces with humidity.

The presence of moisture is known to influence the mixing of particulate solids and could give widely varying results (Abouzeid and Furstenau, 1972; Karra and Furstenau, 1977). Stephenson and Thiel (1980a) prepared ordered mixtures from powders conditioned at 0, 55 and 84% RH and noticed that the rate of formation of an ordered mix was independent of the relative humidity. In a comparison of the

stability of ordered polydispersed sucrose and microfine salicylic acid prepared at different relative humidities, it was shown that mixing at 0 and 84% RH gave more stable mixtures than at 55% RH (Thiel and Staphenson, 1982). The stability at 0% was attributed to electrostatic charging and at 84% to liquid bridging. Staniforth (1985b) in a similar experiment noted that ordered units of pyridoxine and fructose conditioned at 55% RH were more stable than those conditioned at 0% RH. He concluded that the moisture present contributed to the spontaneous granulation of drug and excipient particles through the formation of extremely stable ordered units.

1.3.3 Methods for identifying the formation of ordered units in powder mixes

In certain mixing operations it may be desirable to form ordered mixes to improve the homogeneity or physical characteristics of a dosage form. For such a case the formulator should be able to recognise the formation of ordered mixes and if possible, to quantify the extent to which such a mix has occurred.

The following methods may be used, of which techniques 1-5 have been discussed by Staniforth (1982c):

1. Statistical method
2. Mixing-end point determination method
3. Sieve method
4. Adhesional force measurement method
5. Scanning Electron Microscopy with X-ray analysis
6. UV fluorescence microscopy
7. Permeametry method

1.3.3.1 Statistical method

In ordered mixing, segregation can be avoided by the use of monodisperse carrier particles (Crooks and Ho, 1976; Yip and Hersey, 1977a; Thanomkiat et al, 1979); such a mix may approach an ideal state where the standard deviation is zero when sampled at a size larger than a single ordered unit (Yip and Hersey, 1977b). The measured standard deviation for a perfect ordered mix is therefore independent of sample size above this limiting value.

$$\sigma^2_{OM} = 0 \qquad \text{Equation 1.27}$$

In contrast, random mixtures have variances dependent on the proportions of particles present in the mix and from Lacey's equation, show a gradual reduction in variation as the sample size is increased.

In practice, real perfectly ordered mixes have finite variance due to additive experimental and statistical errors. The measured variance for a perfectly ordered mix, σ^2_{OM}, can be given by:

$$\sigma^2_{OM} = \sigma^2_A + \sigma^2_S + \sigma^2_P \qquad \text{Equation 1.28}$$

where σ^2_A, σ^2_S and σ^2_P are the variances due to analytical and sampling errors and variation in purity of substances used respectively. A number of workers have used the fact that sample variance of a perfect ordered mix is independent of sample size to distinguish the formation of ordered mixes from random mixes. (Yip and Hersey, 1977b; Rees and Staniforth, 1978; Yeung and Hersey, 1979; Stephenson and Thiel, 1980a.) However, during ordered mixing, the mix never reaches the ideal state and furthermore, an unstable mix

is likely to be prone to segregation during sampling; these effects introduce a further error so that the variance of such a mix includes the added variance, σ^2_M.

$$\sigma^2_{OM} = \sigma^2_M + \sigma^2_A + \sigma^2_S + \sigma^2_P \qquad \text{Equation 1.29}$$

Orr (1979) calculated the variance due to experimental errors and pointed out that experimental errors may be large approaching the magnitude of the calculated variance and thus influences the relationship of sample size with measured variance. Furthermore, Lai and Hersey (1981) found that the theoretical relationship was valid only for monosize carrier particles, but invalid for all other types of mixes. Therefore in a random mix where σ^2_R is small, and approaches the magnitude of experimental error, any gain in homogeneity through the formation of an ordered mix will be masked by experimental errors. As a result though the variance - sample size relationship is theoretically correct, it cannot be applied in most cases and another method must be used to confirm the formation of ordered mixes.

1.3.3.2 Mixing-end point determination method

The random mixing of solids requires the dilation of powder bed to allow for free particle movement within the powder mix. Where fines and coarse carriers are to be mixed, the voids created by the packing of the carriers may be large, consequently ordered mixing of fines and coarse particles should be less dependent on bed dilation. It should therefore be possible to differentiate random mixing from ordered mixing on this basis.

The time of complete mixing of any number of components, t', has been related to the time of complete mixing, t, when the mixing vessel is only half-filled with powder (Harvey, 1979)

$$t' = \frac{v}{s} t \qquad \text{Equation 1.30}$$

where v, is the bulk volume of the powder and s, the utilisable free space in the mixer and $v \ll s$. Staniforth (1982c) has tested this relationship experimentally using ordered and random mixes at 50 and 75% fill volume. The predicted relationship between mixing time and fill volume was not found in the random system. For the ordered system, mixing was complete within 6 minutes at 50% fill volume whereas for the 75% fill volume, the sample variance never reached the acceptable level of homogeneity. This was because by increasing the fill volume, the spatial length and duration of each particle movement was reduced.

Powder mixing mechanisms appear to be more complicated than that assumed by the above equation. The type and strength of interparticle attractive force also influence the mixing time. As a result, mixing-end point determination method cannot be used to identify the formation of ordered units in a powder mix.

1.3.3.3 Sieve method

In this method for determining the formation of ordered mixes, the powder mix is placed on a sieve capable of separating the fine powder fraction from coarse carrier particles, and separation is effected by shaking either manually, mechanically or by using an air-jet sifter. Where a perfectly stable ordered mix has been formed no

fines should be collected but in random mixes, virtually all the small particles should pass through the sieve and be collected. In between these two extremes, when partially ordered random mixes are formed, a proportion of the fines can be collected. Therefore, the quantity of fines collected should indicate the degree of ordering or interaction within the mix.

The method is simple and has been widely used in the literature (Travers, 1975; Lai and Hersey, 1981; Soebagyo and Stewart, 1985). However, it has the disadvantage that the applied separation force is not defined and interparticle adhesional forces may vary within and between ordered mixes. Ordered mixes may also appear to be random when in fact a partially ordered random mix or a particularly unstable ordered mix has been formed. Problems of sieving such as clogging of pores, cohesion of powders and charging of the material may reduce the efficiency of the sieving process, thus causing random mixes to appear as ordered.

1.3.3.4 Adhesional force measurement method

Adhesional forces between particles can be measured by applying force to effect separation. The methods which may be used include gravity, centrifugation, and vibration. Staniforth and co-workers (1981) have used the ultracentrifuge technique to determine the magnitude of force in ordered pharmaceutical mixes. In this technique ordered units were held behind a screen, capable of separating fines from coarse carrier particle, in a specially constructed ultracentrifuge rotor tube insert. The tube was rotated

by ultracentrifugation and when the forces generated became greater than interparticle forces, the ordered unit broke down allowing the screen to separate the particles. The fines collected can then be measured by any suitable method. Adhesional force profiles were plotted which relate the adhesional force to the cumulative percentage of drug adhering on the carrier surface.

Two types of profiles were identified. In perfectly ordered mixes, a simple asymptotic curve was drawn which was explained as the gradual break down of ordered units as the centrifugal force was increased. The second type of profile showed two distinct curves linked by a lag period. This was indicative of partially ordered mixes where the weakly bound adherent particles are first removed followed more slowly by the more strongly adhered particles. By setting a limit of percent adhering at an applied force for a perfectly ordered mix, powder mixes of similar formulations can be compared (Staniforth, Rees, Lai and Hersey, 1982). The disadvantage of this system is that where coarse particles with a wide range of particle sizes are used, a large variation in the measured adhesional forces may be noticed. Also there is the added difficulty of handling ordered units and collecting a suitable quantity of adherent which can be accurately analysed.

1.3.3.5 Scanning Electron Microscopy combined with X-ray analysis

The interaction between electrons of suitable energy and a solid substrate may cause the solid to emit X-rays consisting of background X-rays together with characteristic superimposed peaks at discrete energies. The energy or wavelength of these characteristic X-rays is specific for each element and varies with atomic number.

Therefore a particle containing a particular element can be identified by the emitted X-rays (Scott, 1983).

By using Scanning Electron Microscopy (SEM) to obtain photomicrographs of the surface of an ordered unit and comparing with the X-ray image shown as a series of dots, adherent particles in an ordered unit can be identified. Crooks and Ho (1976) have used this technique to identify adherent sulphaphenazole particles on Celutab or Dipac carriers by picking out the major sulphur peak. They counted the number of drug particles adhering on carrier surface by counting dot areas but these areas were obviously unclear and it is known that surface roughness may cause variation in X-ray emissions (Cox, 1983). Rees and Staniforth (1979) also identified potassium sorbate particles by potassium ion emissions and showed that the porous particles of Elcema 250 were able to trap potassium sorbate particles in pores and irregularities on the carrier surface. In contrast, the smoother Dipac particles could carry only very few drug particles.

Although the method has been recognised as having potential for quantitative analysis it has been used only qualitatively so far. Pintye-Hodi et al (1981) attempted to quantify the film formation of magnesium stearate by energy dispersive analysis but were unable to detect lubricant levels in the useful concentration range of less than 1%. The technique is also limited by the fact that the lower end of detection is 1KeV, so that elements lighter than sodium e.g. C, N, O cannot be easily detected.

1.3.3.6 UV fluorescence microscopy

Recently UV fluorescence microscopy has been used to identify ordered units; the method is very similar in some respects to SEM combined with X-ray analysis (Staniforth and Iveson, 1986).

For this purpose, particles must fluoresce when irradiated with ultraviolet light and this therefore limits the application. Drugs which exhibit this behaviour include triamterene and the tetracycline group of drugs. By focusing the UV beam on an ordered unit it is possible to identify individual fluorescing adherent particles. In addition the use of a photomultiplier allows the level of fluorescence to be quantified so enabling different ordered mixes to be compared. The method provides both qualitative and quantitative data quickly and easily and also allows a permanent photomicrographic record to be made.

1.3.3.7 Permeametry method

Merle et al (1979) and Gayot et al (1984) have used the Fisher sub-sieve sizer to study the spatial distribution of powder mixes.

The Fisher sub-sieve sizer employs the air permeametric method to measure the average particle size of powder sample. It is based on the principle that a current of air flows more readily through a bed of coarse powder than an otherwise equivalent bed of fine powder, that is equal in particle shape, apparent volume and percentage of voids but differing in average pore diameter by differences in coarseness, surface roughness and internal porosity of the material.

In the Carmen-Kozeny equation, the pore space of a packed bed of powder can be regarded as bundles of parallel capillaries with a common equivalent diameter through which air flows. The equation is

as follows:

$$d_{sv} = \frac{60,000}{14} \sqrt{\frac{\eta C F \rho L^2 M^2}{(V\rho - M)^3 (P-F)}} \qquad \text{Equation 1.31}$$

where d_{sv}, is the diameter of a sphere having the same external surface to volume ratio as the particle in micrometers; where η, the viscosity of air; C, the conductance of the flow meter in ml s^{-1} per unit pressure; ρ , the sample density in g cm^{-3}; L, depth of powder bed in cm; M, the mass of sample in grams; V, apparent volume of compacted bed in ml and P, the overall air pressure head in g force cm^{-2}.

In the apparatus itself, most of the variables are fixed or controlled such that the equation is greatly simplified and the average particle diameter is indicated by the value of F, or the height of a column of liquid. A sample weight equal in grams to the true particle density is consolidated to known porosity values. At high porosities, the large capillaries swamp the effect of smaller ones and therefore air flow is faster than after further compression where all capillaries tend to have the same diameter. When values of lower porosities are reached, there is formation of aggregates or a closely knit network. The value of porosity which gives the minimum diameter is the optimum and most reproducible.

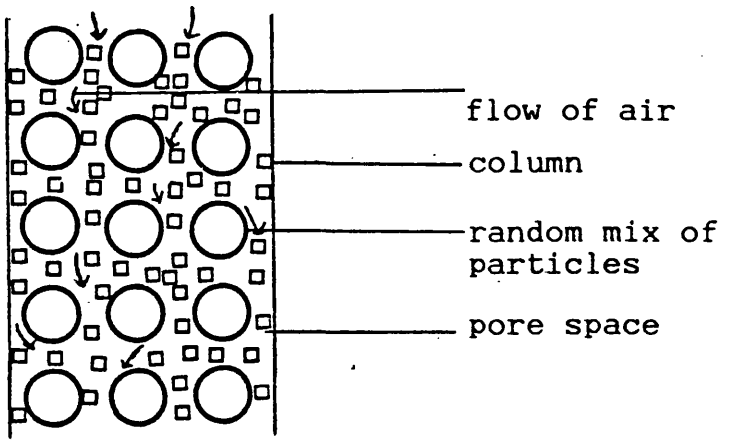
Where there is little interaction between fine powders and coarse carrier, as in random mixing, the flow of air is impeded as the fines fill up the pore spaces and form a powder bed with very fine capillaries (Fig. 1.10a). The measured volume surface mean diameter is then greatly reduced as compared to the packed coarse carrier bed. In contrast where there is interaction between particles

Fig. 1.10 Spatial arrangement and packing of particles in

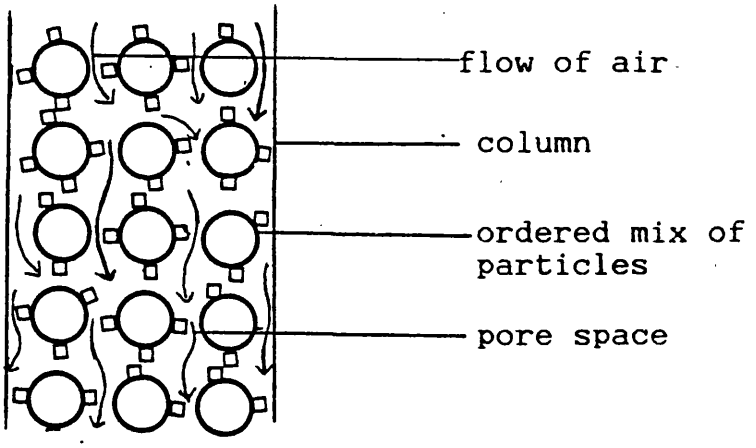
(a) random mix

(b) ordered mix

(a)



(b)



as in an ordered mix, the measured volume surface mean diameter is only slightly reduced or even increased as a highly porous structure still exists (Fig. 1.10b).

The authors Gayot et al (1984) have also successfully used permeametry to explain the behaviour of components in ternary mixtures. When 0.5% magnesium stearate was added to ordered mixes of lactose and 1% salicylate, the measured volume surface mean diameter was increased as the lubricant adhered to the lactose surface. With higher concentrations of magnesium stearate, the salicylate was displaced from carrier surface into pore spaces leading to a decrease in the volume surface mean diameter. They also studied the influence of sequence of mixing and found that for lactose-stearate-salicylate mixtures, the volume surface mean diameters were greater than for lactose-salicylate-stearate mixtures. This indicated that the salicylate had an affinity for the stearate.

It would seem that permeametry is a useful method for determining the spatial structure of components in a powder mix.

1.3.4 Dissolution effects related to mixing

Powders in the pharmaceutical industry are mixed primarily to provide a homogeneous mixture. However, the quality of the mix formed may influence other properties of the solid dosage form such as mechanical strength of tablets, disintegration time and dissolution behaviour.

For binary mixtures, the mix may be random, ordered or more usually any combination of the two as in the total mixes described by Staniforth (1980). When a solid dosage form is produced from such a mix, the final powder structure or the spatial arrangement of the drug and excipients may influence the dissolution and drug release.

Any effect of mixing on dissolution is usually more pronounced in low dose preparations where micronised drugs are often used and the chance of drug-excipient interactions increased. Ampolsuk et al (1974) observed that by spreading 5% $^{w}/_{w}$ digoxin or hydrocortisone over lactose using frictional pressure, higher dissolution profiles were noted than by using either simple blending or solvent deposition. They gave no explanation for these results but Hersey (1974) explained the effect in terms of the introduction of order within the powder mixture. Nystrom and Westerberg (1986) have successfully used ordered mixing of grisefulvin with sodium chloride carriers to improve the dissolution rate of the hydrophobic drug. The adherence of drug to the carrier surface increased the exposed surface area and contact with soluble diluent. After initial fast dissolution of the carrier, the drug is readily and easily dispersed within the dissolution medium. It would appear therefore that when ordered mixing is used to improve dissolution,the solubility of the carrier used must be taken into consideration. Westerberg and others (1986) used both soluble and insoluble carriers to study the effect on drug release. The improvement in dissolution from soluble carriers such as lactose, sodium chloride, and tricalcium dicitrate was much higher than from insoluble Emcompress and glass beads.

Apart from micronised drugs which may form ordered units with carriers during mixing operations, other fine and cohesive excipients may behave similarly. Magnesium stearate is a lubricant which is often added to powder mixes to improve flow and packing characteristics such that a homogeneous mix is transferred uniformly during die compression or encapsulation. It also prevents the adhesion of powders to tooling faces during tableting. The particle size is often between 10-15μm and it lubricates by coating carriers

or substrates. On the question of the extent of ordering or coverage, it was initially thought that a uniform, continuous and monoparticulate layer was formed (Tawashi, 1963a; b). Bolhuis et al (1975) also postulated the formation of a monomolecular film. More recently it is believed that preferential adhesion occurs first to cavities (Bolhuis et al, 1980) followed by a gradual distribution over the substrate surface (Roblot - Treupet and Puisieux, 1986).

The rate of mixing is described by a logarithmic relationship and is proportional to the concentration of the unmixed fine particles (Hersey, 1975). Increased shear also increases the extent of ordering of magnesium stearate on the carrier surface (Shah and Mlodozeniec, 1977; Murthy and Samyn, 1977) and increases the uniformity of the mix. The influence of increased ordering of magnesium stearate on the surface of drug particles will be to increase the hydrophobicity of the drug and to decrease the dissolution rate.

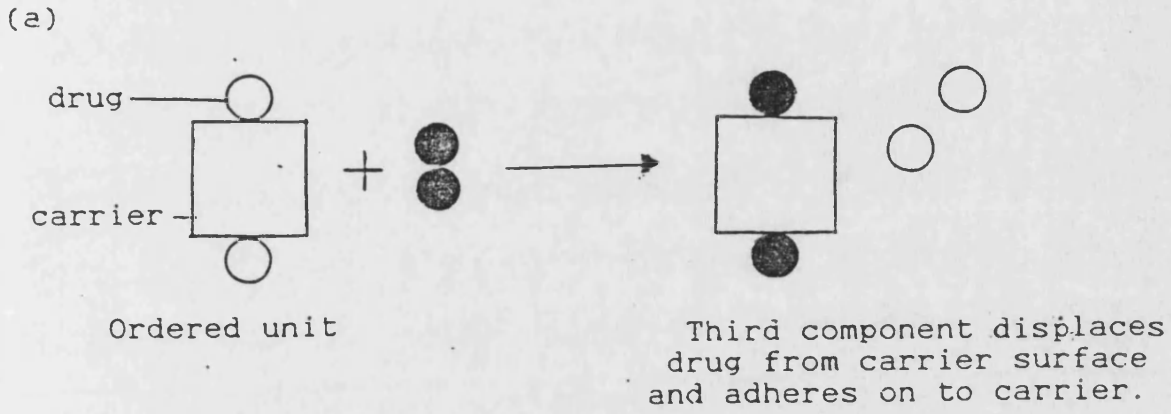
Magnesium stearate has been shown to exhibit considerable batch to batch variation regarding both specific surface area and morphological properties (Butcher and Jones, 1972; Holzer, 1983; Miller and York, 1985). Some workers have found that the influence on dissolution depends on the specific surface area of the lubricant used though they have not explained the effect in terms of the spatial structure of the mix (Frattini and Simioni, 1984). Johansson and Nicklasson (1986) have recently explained this dependency as being related to the free fraction of lubricant in the mix rather than to the final level of surface coverage. Therefore, when mixing magnesium stearate with tablet ingredients the concentration used, the intensity and time of mixing must be taken into account.

Colloidal silica which is used as a glidant may also form a film around carrier particles.

Most pharmaceutical dosage forms contain more than two ingredients. Hersey, Thiel and Yeung (1979) pointed out the possible effects on dissolution where a third component was added to an ordered binary mix and cautioned the use of ordered mixtures in dosage forms (Lai and Hersey, 1979). In one possibility, the third component may adhere preferentially onto carrier particles displacing the original adherent particles from their adhesion sites (Fig. 1.11a). Alternatively, the third component may strip drug particles from the carrier particles but does not bind itself to the carrier (Fig. 1.11b). The effect of the final structure of the mix on dissolution will depend on the role of the components in modifying the release pattern of the dosage form. Magnesium stearate was found to be able to strip salicylic acid from ordered units of sucrose/salicylic acid. Lerk and Bolhius (1977) reported a decrease in dissolution of sodium chloride on the addition of 0.5% magnesium stearate as a result of drug-lubricant interaction. The addition of 2% $^{w}/_{w}$ colloidal silica dislodged lubricant particles from the drug surface and restored the dissolution rate to that of the original blend of sodium chloride with glidant. Johansson and Nicklasson (1986) have also reported similar results but explained the results by suggesting that the colloidal silica interfered primarily with the free lubricant, preventing this free fraction from further coverage on the drug surface.

Bolhuis, Smallenbroek and Lerk (1981) have studied the influence of interaction between tablet disintegrants and magnesium stearate on tablet disintegration. They found that the influence of the lubricant on disintegration or dissolution depended on the swelling capacity of the disintegrant (Lerk et al, 1982). Where the disintegrant was strongly swelling, such as sodium starch glycolate,

Fig. 1.11 Schematic representation of possible effects on the addition of a third component to an ordered unit.



the presence of water set up a chain reaction involving swelling, penetration and finally tablet disintegration so that finally, there was very little effect of lubricant on dissolution. On the other hand, with potato starch, where the swelling was insufficient to eliminate the deleterious effects of the hydrophobic lubricant, tablets exhibited longer disintegration times and slower dissolution rates. Khan, Musikabhumma and Rubinstein (1983) also studied the effect of mixing magnesium stearate with a formulation containing 97 to 99% microcrystalline cellulose, a slightly-swelling disintegrant, and noticed instead a decrease in disintegration time and improved dissolution rate. The authors however did not attempt to explain the results. Chowhan and Chi (1985a) have shown using corn starch and pregelatinized starch, which is a slowly swelling disintegrant, that the influence of the lubricant on dissolution depended on the type of interactions occurring in the total powder mix. With powder mixtures containing drug, lactose and corn starch with magnesium stearate added as the fourth component, adhesion of lubricant occurred on the drug/corn starch units resulting in a marked retardation of dissolution rates. In contrast, where pregelatinised starch was used, no particle - particle interaction occurred and the dissolution from capsules prepared from such blends was not greatly affected by the added lubricant.

In another study, Chowhan and Chi (1986a) found that after thorough mixing of prednisone, dibasic calcium phosphate dihydrate, and potato starch or sodium starch glycolate, only about 70% of the drug dissolved in half an hour due to interaction between the drug and the calcium phosphate. When magnesium stearate was added, the lubricant adhered to drug-diluent units and also to drug particles, and dissolution was reduced further. In contrast when magnesium stearate

was mixed with drug and pregelatinized starch, no inter-particle interactions occurred and dissolution rates were not affected. It would therefore seem that the effect of magnesium stearate on dissolution from solid dosage forms containing disintegrants depends mainly on the type of particle interactions occurring in the total mix and not on the swelling capacity of the disintegrant.

Chowhan and Chi (1985b) also reported that when Ketrolac trimethamine was mixed with cross-linked polyvinylpyrrolidone, crospovidone, drug particles were trapped in voids in polymer particles resulting in lower dissolution rates than for drug alone. On the addition of magnesium stearate, adhesion of lubricant to drug-crospovidone units led to further reduction in dissolution rates (Chowhan and Chi, 1986b). When sodium stearyl fumarate was used instead as lubricant, no particle - particle interaction occurred and neither disintegration times nor dissolution rates were affected.

Thus although mixing may seem at first to be a fairly simple operation, it is important to examine the type and extent of interactions occurring within the total mix. Interactions may occur, for example, between drug and lubricant, drug and diluent, drug and disintegrant or other combinations of formulation components and these may adversely influence dissolution from solid dosage forms.

1.4 AIMS OF THE PRESENT STUDY

Drug substances of low aqueous solubility frequently present problems in the formulation of solid dosage forms that ensure reproducible release and absorption behaviour. In the past, toxic side effects associated with the administration of phenytoin in capsule form were attributed to change in dissolution behaviour when the principal excipient was changed from the insoluble calcium sulphate to lactose (Bochner et al, 1972b; 1973). Recent studies, however, have presented conflicting evidence concerning the role of these diluents and other formulation additives (Carter, 1983).

This project addresses the dissolution behaviour of phenytoin sodium from multi-component systems taking into account factors such as particle size, surface area and other physical and chemical properties of the powder particles. A consideration of factors which might influence drug release from the type of system to be investigated led to the decision that the effect of mixing conditions and spatial arrangement of particles within the total mix should also be evaluated. In order to assess the spatial distribution of components, it was necessary to develop a semi-quantitative method based on SEM combined with X-ray analysis.

2. MATERIALS, METHODOLOGY AND EQUIPMENT

2.1 MATERIALS

2.1.1 Description

The details of the drug compounds evaluated - phenytoin and phenytoin sodium - as well as the two diluents - three sources of lactose and two batches of calcium sulphate dihydrate - and six batches of the lubricant magnesium stearate, are presented in Table 2.1. See footnote below.

2.1.2 Bulk and particle properties of powders

2.1.2.1 Shape and surface characteristics

The particle shape and surface characteristics were determined by Scanning Electron Microscopy using a JEOL 35C scanning electron microscope (Jeol, Tokyo, Japan). Samples photographed represent only a minute portion of the bulk materials and therefore care was taken to select fields of view representative of the various powders. Fig. 2.1a-l shows photomicrographs of the drug, diluent and lubricant powders as supplied.

2.1.2.2 Particle density

The true particle density of drug and excipient powders were determined using a Helium-air pycnometer (Model 1302, Micromeritics Instrument Corporation, Norcross, U.S.A.). The results are shown in Table 2.2 for drug and diluent powders and Table 2.3 for lubricant powders.

footnote

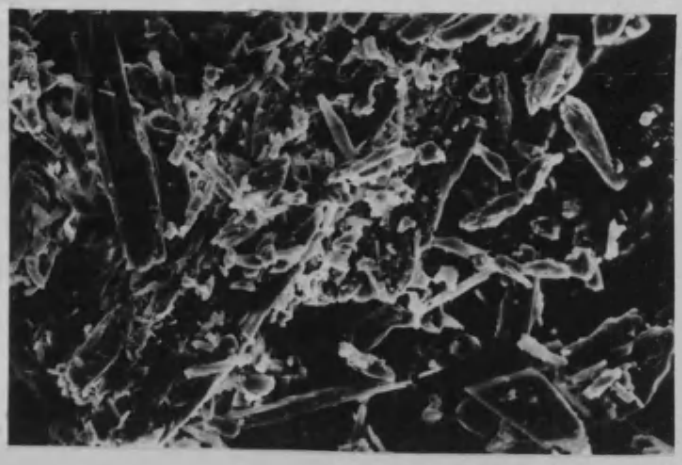
Discrete size fractions of the drug and selected diluent powders were obtained by sieve separation.

Table 2.1 Details of drug, diluents and lubricant powders

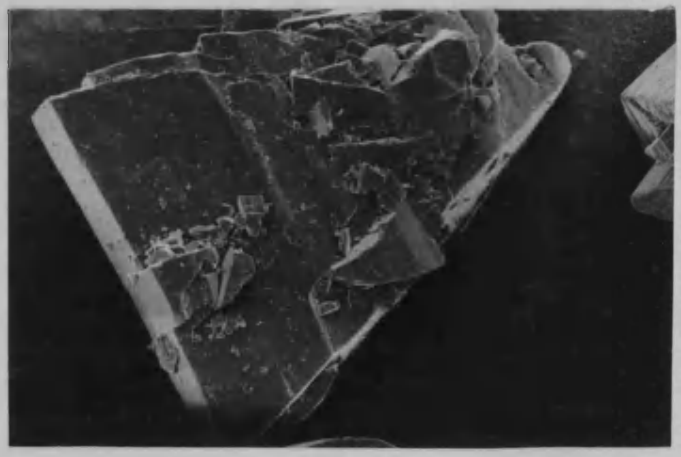
	Powder	Source/Supplier	Batch no.	Symbol
Drug	Phenytoin	Sigma Chemical Co., St. Louis, USA	Lot 124F-0177	-
	Phenytoin sodium	Sigma Chemical Co., St. Louis, USA	Lot 72F-0769	P
Diluents	Lactose (BP)	J.M. Loveridge plc., Southampton, UK	BN 11425	D_1
	Lactose (BP)	Dairy Crest, Thames Ditton, UK	Coarse sample	D_2
	Lactose (BP)	Evans Medical Ltd, Liverpool, UK	7H5877	D_3
	Calcium sulphate dihydrate	British Gypsum, Newark, UK	coarse sample	D_4
	Calcium sulphate dihydrate	BDH, Poole, UK	5584683	D_5
Lubricant	Magnesium stearate	BDH, Poole, UK	93797200	L_1
	Magnesium stearate (GPR)	BDH, Poole, UK	064240	L_2
	Magnesium stearate (BP/EP)	Durham Chemicals Ltd, Birtley, UK	Reference sample	L_3
	Magnesium stearate (BP/EP)	Durham Chemicals Ltd, Birtley, UK	B33	L_4
	Magnesium stearate (BP/EP)	Durham Chemicals Ltd, Birtley, UK	B77	L_5
	Magnesium stearate (BP/EP)	Durham Chemicals Ltd, Birtley, UK	B78	L_6

Fig 2.1 Photomicrographs of drug, diluent and lubricant powders studied.

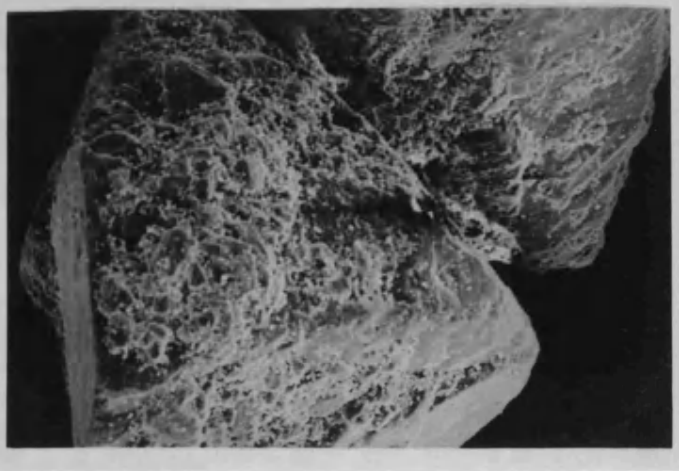
a) Phenytoin sodium-mainly needle-like crystals with few plates.



b) Lactose D_1-individual tomahawk-like crystals with fairly smooth surface.



c) Lactose D_2-individual tomahawk-like crystals with porous surface.



d) Lactose D_3-fine powder; tomahawk-like crystals with fairly smooth surface.

x 2000

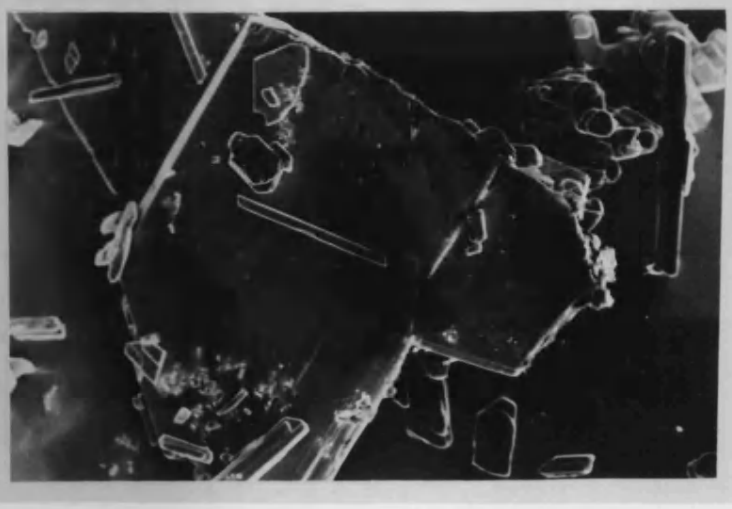
10 um

e) Calcium sulphate dihydrate D_4-individual plate-like crystals with fairly smooth surface.

x 100

100 um

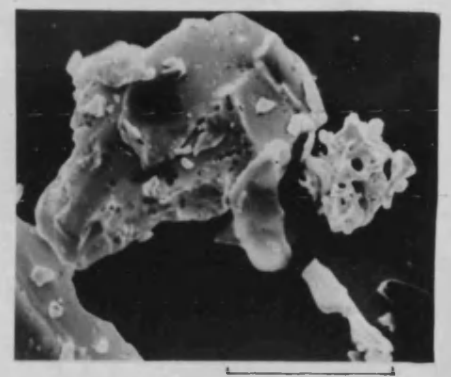
f) Calcium sulphate dihydrate D_5-thin plates and needles with smooth surface.



x 600

10 um

g) Magnesium stearate L_1-large individual plate-like crystals.

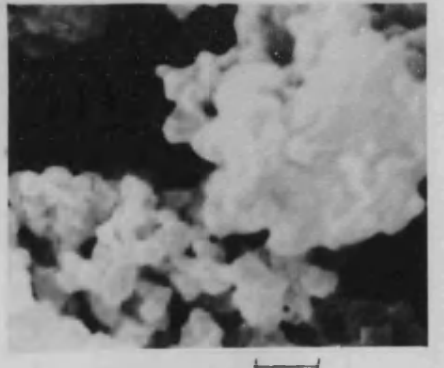


x 2000 10 um

x 7800 1.0 um

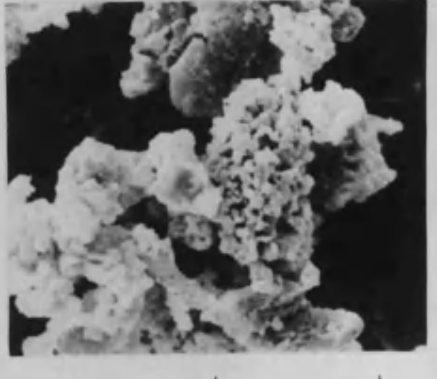
h) Magnesium stearate L_2-mainly plate-like crystals with few needles; particles appear to be agglomerates of fine crystals.

x 2000 10 um



x 7800 1.0 um

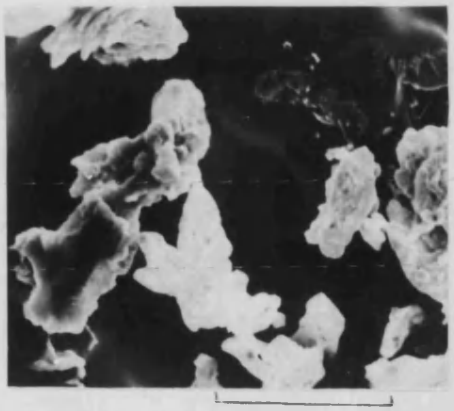
i) Magnesium stearate L_3-plate-like crystals; particles appear to be agglomerates of fine crystals.



x 2000 10 um

x 7800 1.0 um

j) Magnesium stearate L_4-plate-like crystals.



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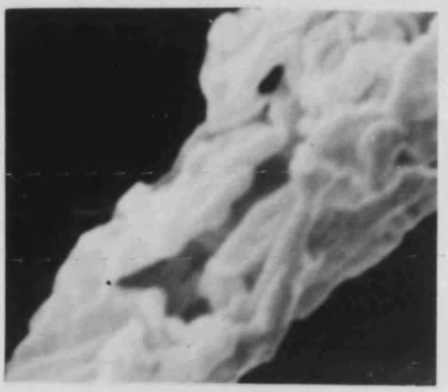

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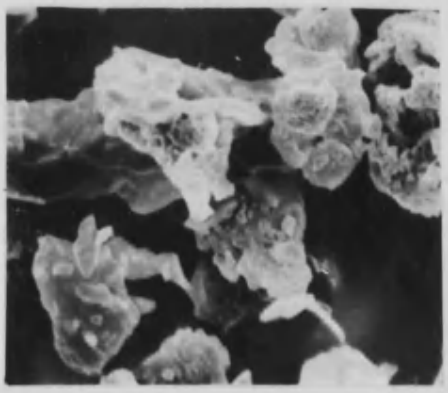
k) Magnesium stearate L_5-plate-like crystals.



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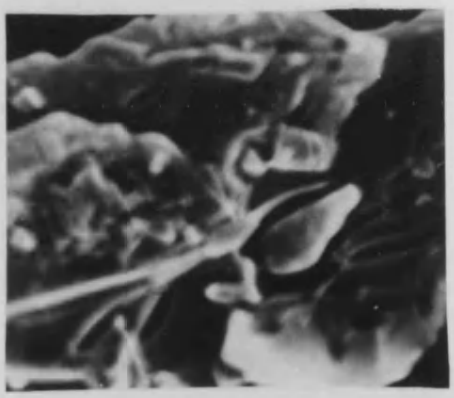

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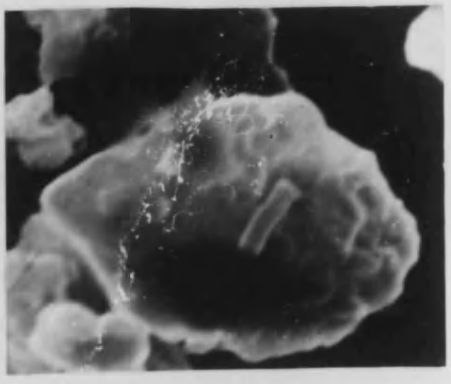
l) Magnesium stearate L_6-plate-like crystals.

x 2000 10 um



x 7800 1.0 um

2.1.2.3 Bulk and tapped densities

Accurately weighed quantities of approximately 5g of each drug and excipient (3g in the case of the lubricants) were poured separately into a 25ml graduated glass cylinder using a glass funnel, and the initial volume recorded. The glass cylinder and its contents were tapped using a jolting volumeter (J. Engelsmann A-G, Ludwigshafen am Rhine, W. Germany). Volume readings were taken after the cylinder had been tapped for 50, 100, 200, 300, 400, 500, 1000, 2000 and 3000 taps. It was found that tapping 3000 times was sufficient to achieve minimum packing volume. It is recognised that the use of a narrow-bore glass cylinder (internal diameter approximately 17mm) provides significant wall effects during vibrating compaction. However, this was used because of the small quantity of powders available and also to simulate the packing conditions within a gelatin capsule shell.

Bulk and tapped densities were calculated and are summarised in Table 2.2 for drug and diluents and Table 2.4 for lubricant powders. The consolidation behaviour of the lubricant powders is shown graphically in Fig. 2.2. The changes in packing density produced on tapping give an indication of the strength of interparticle attractions. Magnesium stearate batch 2 showed the highest overall change indicating the least coherence between particles. Batch 4 showed the least overall change. Normally as particle sizes are reduced attractions between particles increase.

2.1.2.4 Hausner ratio

A measure of the ability of powder to flow can be given by the Hausner ratio: the ratio of the consolidated tapped density to the poured bulk density. The closer the ratio is to a value of one

Table 2.2 Some particle and bulk properties of drug and diluent powders

Powder	Bulk density g ml^{-1}	Tapped density g ml^{-1}	Hausner ratio*	Particle density g ml^{-1}
Phenytoin sodium	0.37	0.69	1.86	1.40
Lactose D_1 <45μm	0.46	0.82	1.78	1.54
90-125μm	0.63	0.82	1.30	1.55
250-355μm	0.65	0.78	1.20	1.54
Lactose D_2 <45μm	0.41	0.68	1.66	1.51
90-125μm	0.48	0.80	1.67	1.54
250-355μm	0.77	0.86	1.12	1.52
Lactose D_3	0.37	0.65	1.76	1.52
Calcium sulphate dihydrate D_4 <45μm	0.63	1.10	1.75	2.30
90-125μm	0.86	1.17	1.36	2.32
250-355μm	1.02	1.20	1.18	2.30
Calcium sulphate dihydrate D_5	0.21	0.45	2.14	2.32

* Hausner ratio : $\frac{\text{tapped density}}{\text{bulk density}}$

Table 2.3 Some physical properties of the six batches of magnesium stearate

Sample	average particle diameter (μm)*	specific surface diameter (μm)	specific surface area (m^2g^{-1})	particle density ($g\ ml^{-1}$)	% loss on drying	surface tension of H_2O soluble extract ($mN\ m^{-1}$)
L_1	-	2.40	2.33	1.07	2.2	63.0
L_2	-	1.40	4.12	1.04	4.6	58.7
L_3	9.88	1.56	3.47	1.11	2.9	67.4
L_4	9.88	1.62	3.40	1.09	2.6	66.6
L_5	12.38	2.70	2.04	1.09	3.2	64.4
L_6	12.38	2.06	2.73	1.10	2.2	65.4

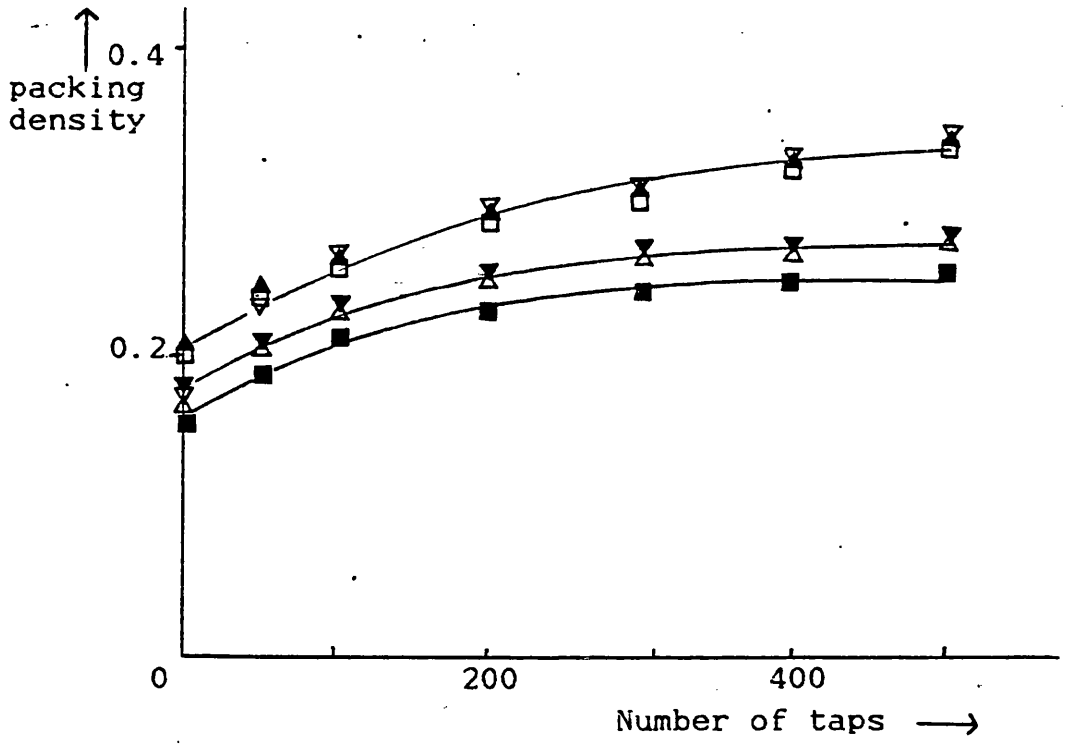
* Data obtained from supplier

Table 2.4 Bulk and tapped densities of the different batches of magnesium stearate

Powder	Bulk density g l^{-1}	Tapped density g l^{-1} (3000 taps.)	Hausner ratio
Magnesium stearate L_1	0.21	0.41	1.95
Magnesium stearate L_2	0.18	0.28	1.56
Magnesium stearate L_3	0.17	0.33	1.83
Magnesium stearate L_4	0.18	0.33	1.83
Magnesium stearate L_5	0.20	0.39	1.95
Magnesium stearate L_6	0.20	0.39	1.95

Fig. 2.2 Changes in packing density produced on tapping the different batches of magnesium stearate

▽ L_1; ▼ L_2; △ L_3; ■ L_4; □ L_5; ▲ L_6.



the better the flow. Powders with poor flow generally have a Hausner ratio greater than 1.25. Results are shown in Table 2.2 for drug and diluent powders and Table 2.4 for the lubricant powders.

2.1.2.5 Specific surface diameter, specific surface area

The Fisher sub-sieve sizer (Kek Instruments Ltd, Manchester, U.K.) is used for the measurement of particle size of powders in the range from 0.2-50 microns. Thus the fine powders phenytoin sodium, diluents D_3 and D_5, and lubricants were characterised by this method. The particle diameter, D_{sv}, obtained is the diameter of a sphere having the same external surface area to volume ratio as the particle. The average particle diameter may also be expressed in terms of the specific surface area, S_w, which is the surface area of the powder per unit mass.

$$S_w = \frac{6 \times 10^4}{\rho D_{sv}} \qquad \text{Equation 2.1}$$

where ρ, is the true particle density of the powder.

The results are shown in Table 2.3 for lubricant powders and Table 2.5 for drug and diluent.

Table 2.5 Specific surface diameter and specific surface area of drug and diluent powders

Powder	particle diameter μm	specific surface area $m^2\ g^{-1}$
Phenytoin sodium (whole fraction)	4.60	0.93
Phenytoin sodium (< 45μm)	3.95	1.08
Lactose D_3	9.70	0.41
Calcium sulphate dihydrate D_5	7.60	0.34

2.1.2.6 Loss on drying

About 1g of each powder as received was accurately weighed into a wide-mouthed sample container. Samples were oven dried at 100-105°C for 3 to 4 hours and the final weight recorded. During reweighing precautions were taken to avoid uptake of moisture. The results for the loss in weight on drying expressed as a percentage of the initial sample weight are shown in Table 2.3 for the different batches of magnesium stearate, and in Table 2.6 for drug and diluent powders.

Table 2.6 Percentage loss on drying of drug and diluent powders

Powder	% loss on drying
Phenytoin sodium	1.40
Lactose D_1	0.1
Lactose D_2	0.1
Lactose D_3	0.2
Calcium sulphate dihydrate D_4	0.1
Calcium sulphate dihydrate D_5	0.2

2.1.2.7 Moisture sorption isotherm

Sorption isotherms at 25°C were determined for drug and diluents D_1, D_2 and D_4 using the particle size fraction 90-125μm. About 1g of powder was placed in a shallow weighing dish in a desiccator in a chamber containing an appropriate saturated salt solution which provided one of a range of required ambient relative humidities. Samples were initially stored at 0% RH until equilibrated, then placed over the appropriate solution. The weight uptake was monitored until no further

increase was observed. Results for moisture sorption for diluent powders are shown in Fig. 2.3 and for phenytoin sodium in Fig. 3.1.

2.1.2.8 Electrostatic charge

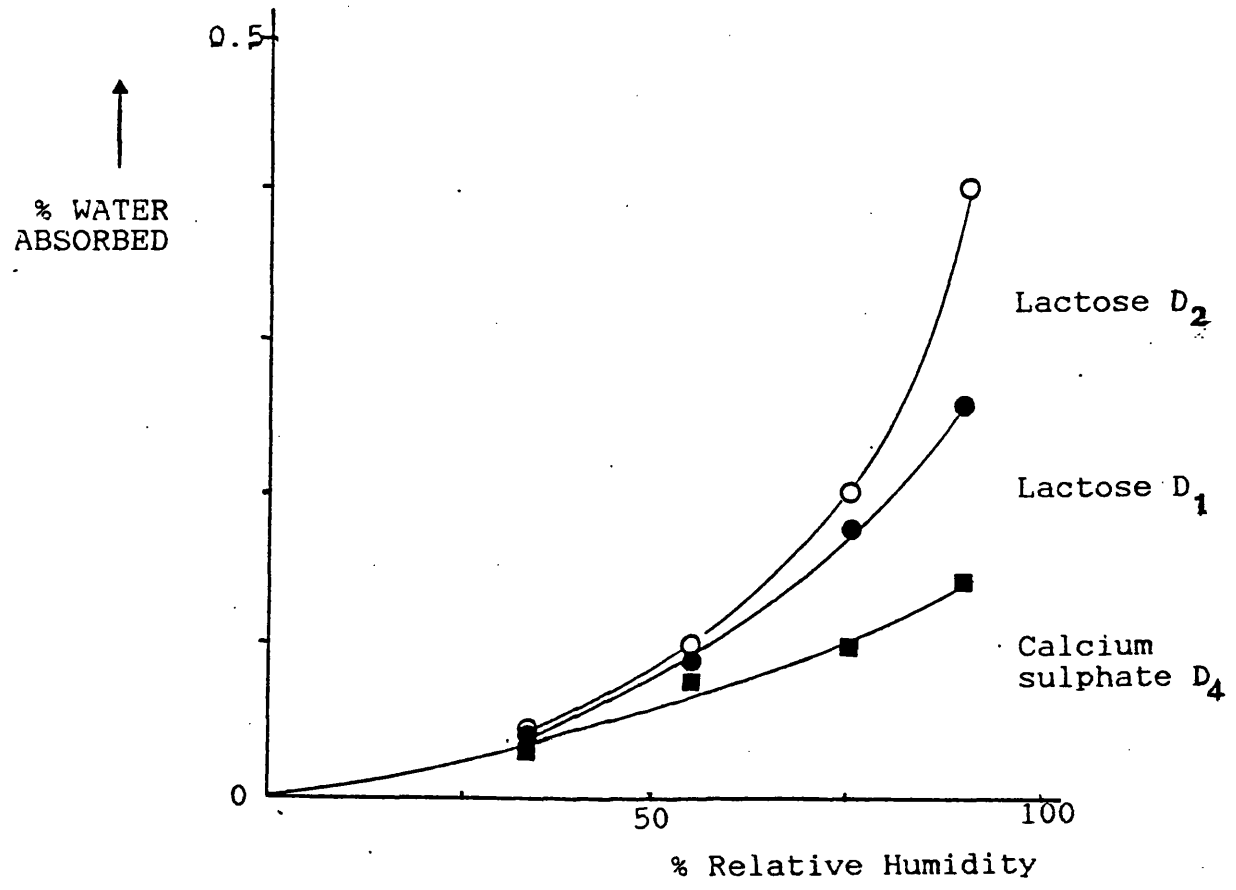
The electrostatic charges developed on powders following contact with a plane metal surface were measured using the method developed by Staniforth and Rees (1982). Each powder was tested individually after storage under ambient conditions for at least 2 weeks in a polyethylene bag. The charge on the powder was measured by allowing the material to flow at a constant rate of approximately 0.4g s^{-1} off a stainless steel surface into a Faraday well static charge detector connected to an electrometer (Type 610C, Keithley Instruments, Cleveland, U.S.A.). Five determinations were made for each powder. The mean specific charge developed and coefficient of variations are summarised in Table 2.7.

Table 2.7 Mean specific charge developed on drug, diluent and lubricant powders on contact with a stainless steel surface

Values in brackets indicate the coefficient of variation (Five determinations each)

Powder sample	Mean specific charge (10^{-9} $C_{\bar{g}}^{-1}$)
Phenytoin sodium	-1.61 (0.17)
Lactose D_1 (250-355μm)	+0.55 (0.03)
Lactose D_2 (250-355μm)	-1.54 (0.08)
Lactose D_3	+4.94 (0.15)
Calcium sulphate dihydrate D_4 (250-355μm)	-1.81 (0.08)
Calcium sulphate dihydrate D_5	-1.05 (0.03)
Magnesium stearate L_1	+3.49 (0.03)
Magnesium stearate L_2	+3.82 (0.04)
Magnesium stearate L_3	+14.04 (0.18)
Magnesium stearate L_4	+15.49 (0.15)
Magnesium stearate L_5	+13.37 (0.17)
Magnesium stearate L_6	+ 4.19 (0.04)

Fig. 2.3 Moisture sorption isotherm for diluents D_1, D_2 and D_4



2.1.3 Physico-chemical characteristics of powders

2.1.3.1 Surface tension of water soluble impurities of magnesium stearate

A 5 g sample of each different batch of magnesium stearate, was shaken in a 250ml conical flask with 100ml freshly prepared double distilled water for six hours. The flasks had previously been cleaned with freshly prepared chromic acid (USP XX/NF, 1980) and rinsed thoroughly with freshly prepared double distilled water. The suspension was allowed to stand and settle for 18 hours and then filtered through a 0.45μm Sartorius filter. Surface tension was measured by the Wilhelmy Plate method at 25°C in triplicate. A blank determination using double distilled water gave a reading of 71.6 mN m^{-1}. Results are shown in Table 2.3

2.1.3.2 Infra-Red spectra

About 1mg of phenytoin and separately of phenytoin sodium was triturated with approximately 300mg of potassium bromide. The potassium bromide had previously been dried over silica gel to remove residual water. After grinding the mixture thoroughly, each powder sample was spread uniformly in a die 13mm in diameter and compressed at approximately 98,100N to form a disc. The disc was mounted in a holder and the IR spectrum from 2.5 to 1.5 μm (4,000 to 670 cm^{-1} wave number) wavelength was recorded using an Infra-Red spectrophotometer (Model 782, Perkin-Elmer, Beaconsfield, U.K.). Results obtained are shown in Fig. 3.2.

2.1.3.3 X-ray powder diffraction

Ground powder samples were exposed to nickel filtered copper K α radiation from an X-ray generator (Philips PW1730, Cambridge, U.K.) operated at a potential difference of 40kV and a current of 20mA. The diffracted X-rays from the powders were detected using a Xenon proportional counter (Philips type PW 1965) mounted in a vertical X-ray diffractometer goniometer (Philips type PW 1080) and scanned at a rate of 2θ per minute. Pulses from the counter were amplified and analysed using a Philips PW 4620 ratemeter/channel analyser and plotted via a chart recorder.

The conditions for refraction are given by the Bragg equation:

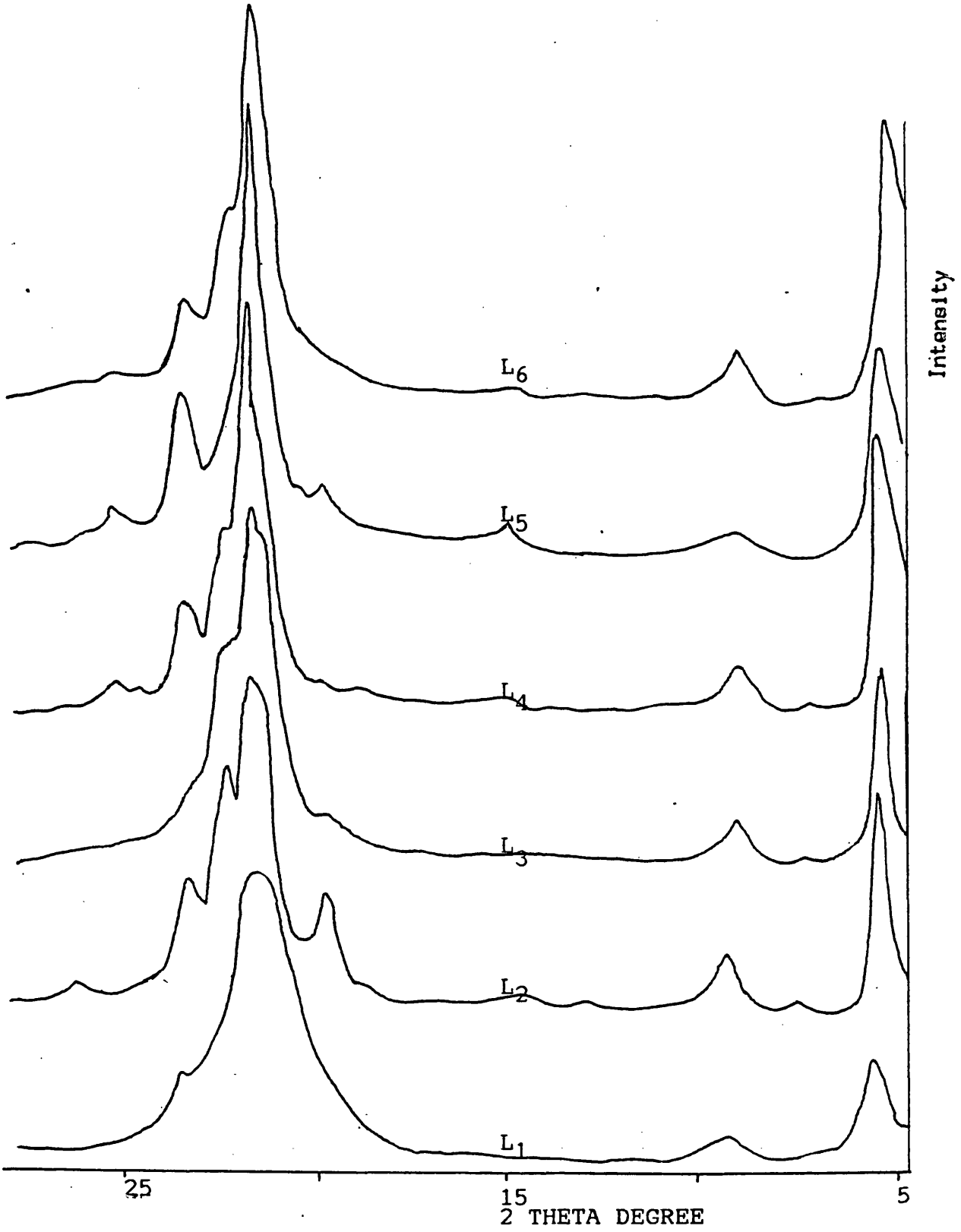
$$n\lambda = 2d \sin \theta \qquad \text{Equation 2.2}$$

where n, is the diffraction order (n = 0, 1, 2....); λ, is the wavelength of the incident X-rays in this case 1.5418Å; d, the distances between the atomic planes in Å; and θ, the angle of incidence and also of refraction of X-ray. The powder diffraction patterns for the magnesium stearate powders are shown in Fig. 2.4. All the batches of magnesium stearate show low levels of molecular order.

2.1.3.4 Differential Scanning Calorimetry (DSC)

3-5mg samples of phenytoin and phenytoin sodium (in the dried and hydrated states) were accurately weighed into aluminium pans and sealed by crimping. The samples were heated in a Differential Scanning Calorimeter (910 DSC, Dupont (U.K.) Ltd, Stevenage, U.K.) and results analysed by a computer/thermal analyser (Model 9900, Dupont (U.K.) Ltd, Stevenage, U.K.). The experimental conditions were; nitrogen gas flow : 30ml/min; heating rate : 5°C/min and the instrument was calibrated using the melting point of indium as standard. The DSC apparatus records

Fig. 2.4 X-ray powder diffraction data for the six batches of magnesium stearate



directly the difference in heat flux or power required to maintain the same temperature in the sample and reference system at the set heating rate. Results are shown in Fig. 3.3.

2.1.3.5 Swelling capacity

It was noted that compacted beds of phenytoin sodium expanded on contact with water with the evolution of heat. To measure the swelling observed, an accurately weighed quantity of drug was filled into a 5ml measuring cylinder and packed to a volume 2.5 cm^3. Powder bed porosity was varied by increasing the powder mass. About two millilitres of water at room temperature, sufficient to wet the powder mass was slowly added to the consolidated powder bed and the increase in volume noted after 5-10 minutes. Several different aqueous wetting solutions were also studied (Table 3.5), the solutions were chosen to simulate possible conditions within a capsule during dissolution testing of formulations evaluated later. A photomicrograph of the wet powder mass were taken with an optical microscope (Zeiss Ultraphot, Carl Zeiss Ltd, Welwyn Garden City, U.K.), and is shown in Fig. 3.7.

Binary blends of drug and diluent powders of size fractions 250-355μm were also studied. It was noted that when the diluent concentrations exceeded 29% $^{w}/_{w}$, no significant swelling occurred, but the addition of aqueous solutions caused drug particles to percolate to the bottom of the glass tube. Furthermore when lactose was used as diluent, dissolution of the lactose particles occurred so that volume readings after wetting the powder bed were much less than the value for powder beds of drug alone. The swelling capacity, S_c, was calculated as:

$$S_c = \frac{\text{final volume - initial volume}}{\text{initial volume}} \qquad \text{Equation 2.3}$$

The porosity or percentage fractional voidage, ϵ, in the consolidated powder bed is given by:

$$\epsilon = 1 - \frac{M}{\rho V} \qquad \text{Equation 2.4}$$

where M, is the powder mass in glass tube; V, the initial packed volume and ρ, the particle density. Results showing the variation in swelling capacity of a bed of phenytoin sodium as a function of porosity are shown in Fig. 3.5.

2.1.3.6 Swelling force

The force created during the swelling of a packed bed of phenytoin sodium when wetted by water was measured using a 100N load cell (Grade B) in conjunction with a mechanical testing instrument (Type T22K, JJ Lloyd Instruments, Southampton, U.K.) operated in compression. A 300mg sample of phenytoin sodium was compacted in a 12.7mm diameter tableting die using a piston attached to the load cell. The lower face of the die rested on a glass sinter of a "Baumann-type" apparatus previously used by Baumann (1966) to measure the liquid uptake of a powder bed. Fig. 2.5 shows the design of the apparatus used. The thickness of 5 representative samples of compact was measured with a micrometer screw gauge. Water at room temperature was introduced into the glass beaker connected, via a capillary tube, with the glass sinter. The height of the piston in the tablet die was held constant as water uptake and swelling occurred; this enabled the force exerted against the piston, that is the swelling force, to be detected and stored by an in-house data acquisition system (Model B, BBC, Acorn Computer Ltd, U.K.). When initial wetting of the glass sinter occurred there was at first, a decrease in the force exerted on the piston. Swelling forces were calculated as the difference in value

Fig. 2.5 Design of apparatus to measure swelling force

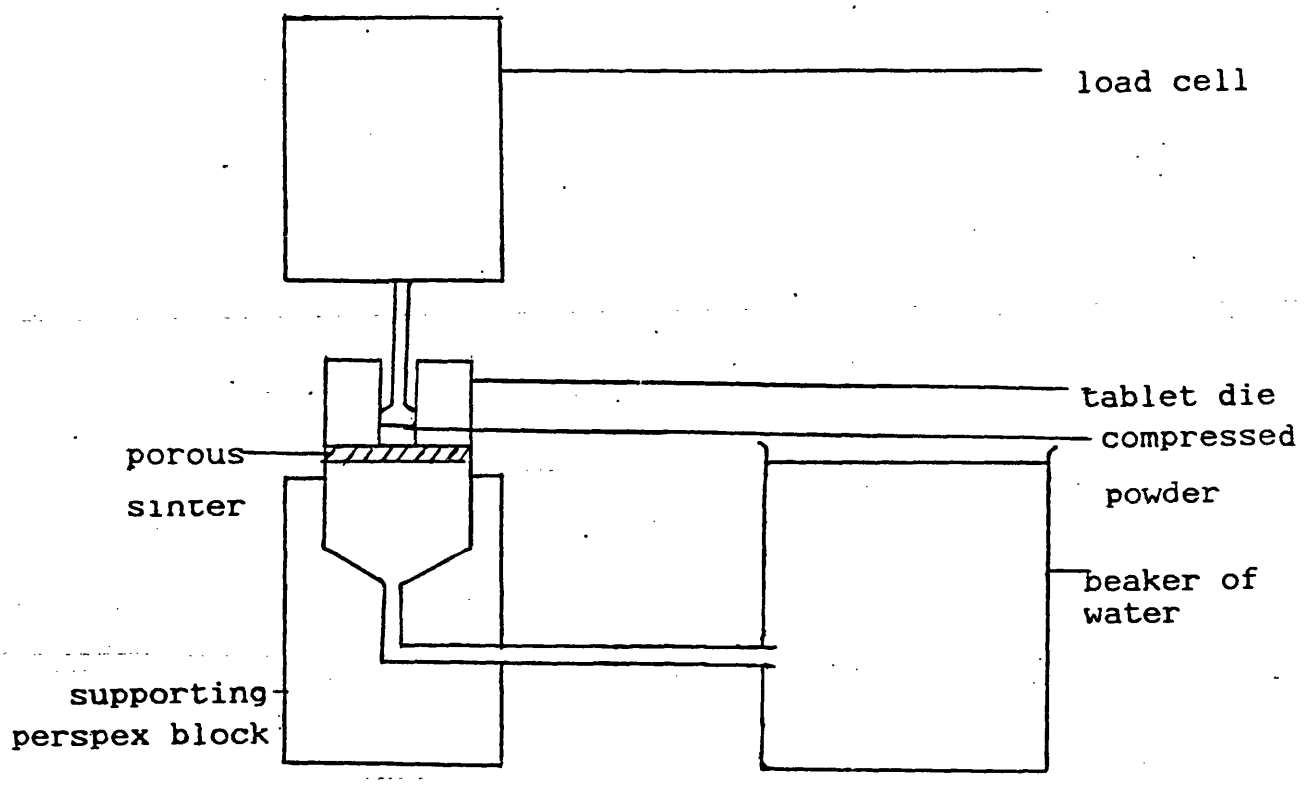
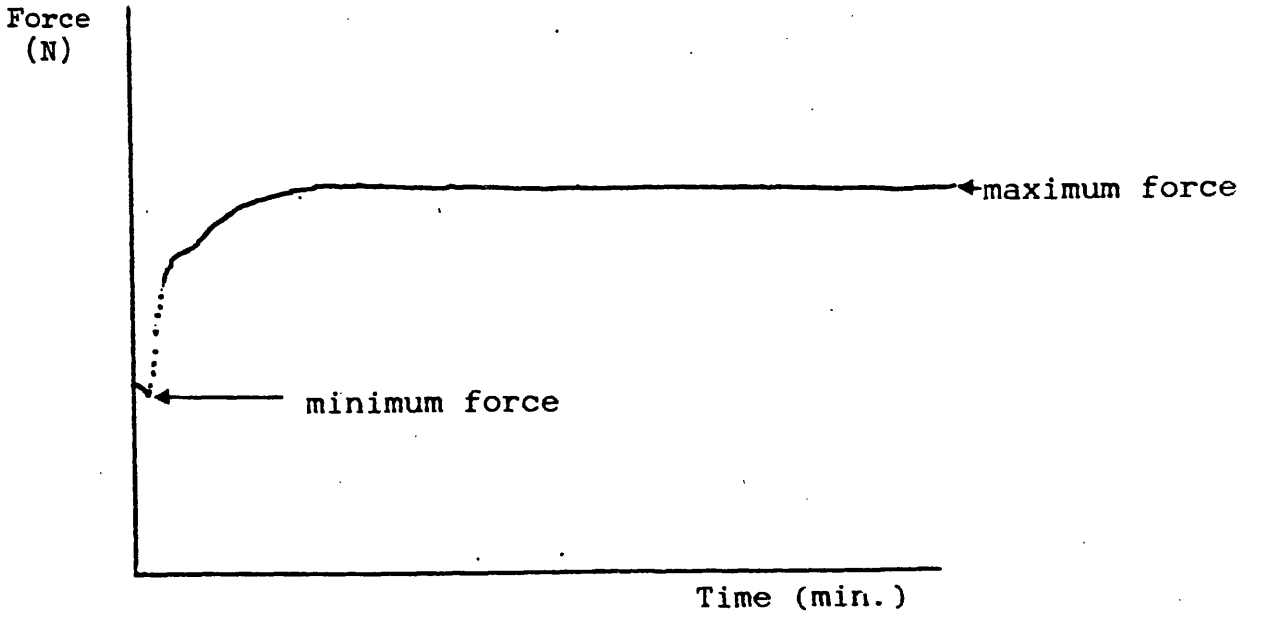


Fig. 2.6 Force versus time profile recorded when wetting phenytoin sodium powder compact



Load cell max	100 N
Load cell magnification	0.1
Init. force	3.3 N
Peak force	6.7 N
Min. force	3.1 N

between the maximum force exerted and the minimum force recorded. Fig. 2.6 shows a typical plot obtained. Three determinations were made at each force and results are shown in Fig. 3.6 for variation of swelling force with porosity within compacted powder bed.

2.1.3.7 Solubility

The solubilities of phenytoin sodium, phenytoin and diluent powders were determined using a dissolution test rig (Model 6ST, GB Caleva, Sunninghill, U.K.). Excess powder was weighed into a dissolution vessel containing 500ml of freshly distilled water at 25°C and stirred by means of a paddle. Samples were taken and assayed until no change in concentration with time was observed.

Calcium sulphate solutions were assayed by titration with 0.01M disodium edetate VS (USP) using Erichrome Black T indicator. Lactose solutions were analysed refractometrically using 2 dm cells with sodium D-line (Model AA-10, Optical Activity Ltd, Ramsey, U.K.). The specific rotation α_D for lactose D_1 and D_2 were 52.5 and 52.2° respectively which is within the limits set by the BP (52.2-52.8°). Phenytoin solutions were analysed by UV spectrophotometry at 232nm (Model 733, Perkin Elmer, Beaconsfield, U.K.). Table 3.3 shows the equilibrium solubility values for the drug and diluent powders.

2.2 METHOD AND EQUIPMENT

2.2.1 Preparation of powder mixes

The required quantity of each powder component was accurately weighed to 4 decimal places (Oertling Balance, Oertling Ltd, Orpington, U.K.) on to a sheet of paper. The components were then mixed by serial dilution using a nickel spatula to shear the powders on the plane paper surface. In the case of two-component mixes, mixing was carried out for 5 minutes and a further 5 minutes was added where a third component was added. The total powder weight of powder handled in each mix was limited to 2-3g; the objective was to ensure a reproducible process involving extensive interparticle movement without the risk of size reduction. The procedure was standardised to minimise errors due to operator variations.

In order to evaluate the effect of particle size on mixing behaviour, phenytoin sodium, lactose D_1 and D_2 were fractionated by sieving according to BS 1796 (1976). Calcium sulphate D_4 received from the manufacturer was a relatively coarse sample of size range 250-850μm, therefore to obtain the various particle sizes of interest, the coarse sample was ground using a mortar and pestle, and fractionated by sieving. For each diluent, three size fractions were collected: $<45\mu m$; 90-125μm and 250-355μm.

2.2.2 Preparation and storage of capsules

The appropriate powder or powder mix was filled into colourless transparent hard gelatin capsules (size 2, Davcaps, Gwent, U.K.) by tamping the capsule body into a powder bed until the desired weight had been obtained. The cap was then applied to the body and the shell was gently rotated to distribute the powder throughout the capsule shell.

Dissolution testing was carried out immediately, except for capsules where the effect of prolonged storage and relative humidity was to be tested, when the capsules were stored in a desicator over silica gel or over saturated solutions of appropriate salts, to provide relative humidities of 0, 55 or 86%. Capsules were stored for 1, 2, 4 or 8 weeks before dissolution testing was carried out. Moisture uptake or loss for the empty or filled capsules were also monitored by weighing and results are shown in Table 3.10.

2.2.3 Dissolution studies

2.2.3.1 Assay of phenytoin

Phenytoin has no specific UV absorption in acidic or alkaline medium. A low absorptivity at 256nm, typical of benzenoid drugs implies that assays could not be performed at that wavelength. By the use of second-derivative spectroscopy a wavelength minimum was found at 232nm, which occurs on a shoulder of the absorption spectra and explains why some workers (Neuvonen et al, 1977; Dunn, 1982) have found it suitable for assay of phenytoin.

To determine the Beer-Lambert's relationship for phenytoin sodium, solutions of 100mg phenytoin sodium in 1000ml standard borate buffer pH 9.0 (BP, 1980) were prepared. Absorbance readings were taken on a 733 Perkin Elmer spectrophotometer using 1cm matched cells. Dilutions were made such that the absorbance readings fell within the 0.05 to 0.7 absorbance units. The range was extended to 0.05, although this is outside the limit for maximum sensitivity, because of the low concentrations of phenytoin for which certain analyses were required; for example, formulations containing a high proportion of diluent. The solutions were sampled and filtered through a 0.45μm Sartorius filter after initially checking that the

filter was inert and did not cause adsorption of the drug. Fresh solutions in borate buffer were prepared by shaking 100mg of the phenytoin sodium with gelatin capsule shell, and either 1.9g of lactose or calcium sulphate dihydrate to confirm that these formulation components neither contributed to the UV absorption nor adsorbed the drug from solutions. Solutions were also prepared to contain 130mg lactose or calcium sulphate dihydrate and 5% magnesium stearate. Similar solutions were prepared containing either 130mg calcium chloride (Fisons Scientific Equipment, Loughborough, U.K.) or dibasic calcium phosphate dihydrate (Emcompress, Edward Mendell Inc., New York, U.S.A.). Correlation and regression analysis were carried out on the results to obtain the gradient of the slope and the percentage absorption coefficient, $E^{1\%}_{1cm}$ (Table 2.8).

The presence of diluents did not contribute significantly to the absorbances observed and the Beer-Lambert's relationship was obeyed in the concentration range from 0.25 to 3.0 x 10^{-3}% $^{w}/_{w}$. The $E^{1\%}_{1cm}$ value for phenytoin sodium in borate buffer was 210. A similar procedure was followed for phenytoin using instead 92mg phenytoin. The $E^{1\%}_{1cm}$ value for phenytoin was 236.

2.2.3.2 Apparatus suitability testing

The USP requires that the equipment for dissolution testing is tested for performance using two types of dissolution calibrators. The dissolution apparatus used (Model 6ST, GB Caleva, Sunninghill, U.K.) consists basically of a rotating paddle and a round-bottomed one-litre dissolution flask in a water bath. Specifications for the dissolution apparatus are given in the USP (1980). The calibrators are a disintegrating prednisone tablet and a non-disintegrating salicylic acid tablet.

Table 2.8 Beer-Lambert's relationship for phenytoin sodium solutions

% conc. x 10^{-3}	Absorbance of phenytoin sodium solutions				
	after filtration	with 1.9g lactose	with 1.9g $CaSO_4 2H_2O$	with 130mg $CaCl_2$	with 130mg Emcompress
3.0	0.631	0.630	0.634	0.632	-
2.5	0.525	0.524	0.532	0.531	0.532
2.0	0.420	0.420	0.425	0.425	0.426
1.5	0.318	0.317	0.318	0.319	0.321
1.0	0.208	0.209	0.220	0.221	0.221
0.5	0.104	0.106	0.112	0.112	0.112
0.25	0.055	0.054	0.056	0.055	0.056
correlation coefficient, r	0.999	0.999	0.999	0.999	0.999
Gradient of slope $E^{1\%}_{1cm}$	210.0	209.5	209.6	209.1	210.4

For prednisone tablets (Lot F, Glaxo, Ware, U.K.), the dissolution apparatus was operated at 50 and 100 rpm using 900ml of deaerated water at 37 $\pm$ 0.5°C. Samples were taken at 30 minutes and the drug content was determined by UV analysis at 242nm. Dissolution testing of salicylic acid calibrators (Lot G, Glaxo, Ware, U.K.) was carried out in 900ml of 0.05M phosphate buffer pH 7.4 $\pm$ 0.05 (USP, 1980) and assayed at 296nm by UV analysis. Six replicate measurements were performed simultaneously for each formulation.

The apparatus was found suitable since the individual values calculated for prednisone tablets fell within the ranges 51-77% at 50 rpm and 68-85% at 100 rpm as specified by the USP. For the salicylic acid tablets, the average for the six replicates were within the 14-23% with standard deviation less than 4% at 50 rpm and within 17-30% with standard deviations also less than 4% at 100 rpm.

2.2.3.3 Method

The dissolution medium used was freshly prepared deaerated standard borate buffer pH 9.0. The pH of the solution was checked to within 0.05 units with a pH meter (Model PW 9410, Pye Unicam Ltd, Cambridge, U.K.) before use. One litre of the dissolution medium was placed in each of the dissolution vessels and equilibrated to 37 $\pm$ 0.5°C. Capsules weighted by copper helical coils of uniform weight were dropped into dissolution vessels and the rotation of the paddles at 50 rpm was started immediately. Initial studies at higher rotational speeds showed that agitation conditions were too severe leading to lack of discrimination between formulations. At 5, 10, 15, 30, 45, 60, 90 and 120 minutes or other suitable intervals, 10ml samples were removed through a stainless steel cannula using a syringe. The sample

removed was filtered through a 0.45 μm Sartorius filter to remove undissolved drug particles. Each sample removed was replaced with fresh dissolution medium at 37 ± 0.5°C to keep the volume in the vessels constant. Dissolution was carried out to completion for each test and 5 capsules were tested for each formulation. The amount of drug in each sample was determined spectrophotometrically, after dilution when necessary, at 232nm using 10mm matched cells.

During the dissolution run with formulations containing phenytoin sodium, a slowly dissolving precipitate was observed to form at the bottom of the vessel. Using IR and SEM combined with X-ray analysis, this precipitate was identified as phenytoin. The precipitate was already formed within 5 minutes of commencing the dissolution run. To further elucidate the magnitude of this effect, dissolution testing was stopped at 5 minutes and the quantity of phenytoin assayed. The precipitate from all five vessels was collected by allowing all aggregates from dispersed capsule contents to settle, carefully decanting as much of the dissolution medium as possible and transferring the suspension to a 160ml separator. Phenytoin was extracted and assayed according to the USP (1985) method. Extraction was achieved with 20ml of a 1 in 2 parts mixture of ether in chloroform and completed with 10ml successive portions of the ether-chloroform mixture until a small portion of the extract did not leave a residue when evaporated on a watch glass. The combined extract was shaken, filtered and the filtrate was dried in a rotary evaporator under vacuum (R110, Rotavapour, Buchi, U.K.). The phenytoin content was assayed titrimetrically by dissolving the dried extract in 25ml dimethyl formamide, adding 3 drops of azo-violet indicator and titrating with 0.01N sodium methoxide VS to a blue end-point. Precautions were observed against the absorption of atmospheric carbon dioxide. Each

ml of 0.01N sodium methoxide is equivalent to 2.52mg of phenytoin. The results are shown in Fig. 3.14.

For capsules containing calcium sulphate dihydrate as diluent, diluent particles were undissolved after 60 minutes of dissolution testing. To check if any phenytoin had been adsorbed on to the surface of the diluent, a sample of the undissolved diluent was taken, washed carefully with distilled water and vacuum dried at 60°C. The calcium sulphate particles were then examined by SEM combined with X-ray analysis. The method is discussed under Section 2.2.4 and results shown in Fig. 3.15.

2.2.3.4 Mixing and formulation factors evaluated

Capsule formulations of phenytoin sodium or phenytoin were prepared in various ways to study the effect of the following formulation and processing variables on in-vitro dissolution.

I Single-component formulations:

(i) The effect of increased packing density of phenytoin sodium in a capsule on dissolution was studied by increasing the fill weight of capsule from 50 to 400mg.

(ii) The effect of phenytoin sodium particle size on dissolution was evaluated using sieve-sized fractions less than 45μm, 63-90μm, 90-125μm and 125-180μm. The fill weight of capsules was 300mg.

(iii) The effect of prolonged storage at various humidity levels on dissolution of capsules was studied on capsules containing 300mg of phenytoin sodium. Capsules were stored at 25°C for 0, 1, 2, 4 and 8 weeks at either 0, 55 or 86% relative humidity.

II Two-component formulations

(i) The effect of diluent type was studied on dissolution of capsules containing 100mg phenytoin sodium and 130mg diluent. The diluents used were lactose D_3, calcium sulphate dihydrate D_5, dibasic calcium phosphate or calcium chloride. The calcium salts were chosen to provide a range of calcium diluents of varying solubilities.

(ii) The effect of diluent type was studied on the dissolution of 92mg phenytoin and 119mg diluent. This was done to compare the effect of change in chemical form of the drug from the sodium salt to the free acid.

(iii) The effect of increasing the proportion of diluent (lactose D_1, D_2 or calcium sulphate D_4) on the dissolution of phenytoin sodium. The two diluents were chosen from those used in II(i) as model soluble and insoluble diluents. Capsule fill weight was maintained at 300mg.

(iv) The effect of particle size of the different diluents was also studied. Sieved size fractions of diluents less than 45μm, 90-125μm and 250-355μm were used.

(v) The effect of humidity and storage on the dissolution of phenytoin sodium capsules containing 70mg phenytoin sodium and 130mg diluent. Diluents used were lactose D_1 or calcium sulphate D_4 and particle size was 250-355μm.

III Three-component formulations:

(i) The effect of increasing concentration of magnesium stearate L_1 (0.05%, 0.5% and 5% $^{w}/_{w}$) on the dissolution of phenytoin sodium from capsules containing 100mg drug and 130mg of the different diluents lactose D_3 or calcium sulphate D_5.

(ii) The influence of magnesium stearate from different batches and sources on the dissolution of phenytoin sodium from capsules containing 100mg drug, 130mg diluent (lactose D_3 or calcium sulphate D_5), and 12.1mg (i.e. 5%) magnesium stearate.

(iii) (a) The influence of mixing sequence on the dissolution from capsules containing 100mg phenytoin sodium, 130mg diluent (lactose D_3 or calcium sulphate D_5) and a range of lubricant concentrations (0.05, 0.5 and 5.0% $^{w}/_{w}$). Where lubricant (L) was added to a binary blend P-D, of phenytoin sodium (P) and diluent (D), the mixing sequence is referred to as P-D-L. When diluent was first in contact with lubricant the sequence is described as D-L-P, whilst the code P-L-D refers to the case where the lubricant was first mixed with the drug.

(iii) (b) To exaggerate some of the differences observed in dissolution, study III(iii)(a) was extended to use fine drug particles ($<45\mu m$) and a coarse size fraction (250-355μm) of diluent. The diluent proportion was varied from 0 to 95% $^{w}/_{w}$.

2.2.3.5 Treatment of results

From the absorbance readings the concentration of drug in each dissolution test sample was calculated using the Beer-Lambert's relationship,

$$A = E^{1\%}_{1cm} \cdot c \cdot 1 \qquad \text{Equation 2.5}$$

where A, is the absorbance; $E^{1\%}_{1cm}$, the percentage absorption coefficient; c, the concentration and 1, the pathlength. As successive samples were taken from the vessel, the actual concentration of drug dissolved had to be corrected by adding the concentration of the sample withdrawn

previously. The dissolution profile was followed by plotting the percentage drug dissolved against time. The percentage dissolved in 30 minutes was recorded as W_{30}, as it was found to discriminate satisfactorily between the formulations used. Results were then assessed by analysis of variance. The results were also treated according to the method of Kitazawa et al (1977) whereby $\log_e \frac{W_\infty}{(W_\infty - W_t)}$ is plotted against time. W_∞, represents the amount dissolved at complete dissolution; W_t, the amount dissolved at time, t; and $W_\infty - W_t$, the amount undissolved at t.

2.2.4 Scanning Electron Microscopy with X-ray analysis

In SEM a fine beam of electrons 5-50 keV is caused to scan across a sample, these electrons interact with samples producing secondary electron emissions, back scattered electrons, X-rays, light or cathodluminiscence. The X-rays emitted consist of background X-rays which are produced as a result of Coulombic interaction and characteristic X-rays which are the result of inner-electron ionisation. Since the electronic interactions involve electron orbitals of discrete energies, which are specific for a particular element, the emission of a particular X-ray can be used for the detection of a particular element in a sample. Normally K_∞ radiations are used for analysis of elements with atomic number 11 up to 32. The relative intensities of the characteristic X-rays depend on the mass fractions or concentrations of the emitting elements and therefore provide a basis for quantitative analysis. This is normally done by the measurement of the absolute X-ray intensity from the unknown and comparing this measurement with the absolute X-ray intensity from a suitable standard made under identical instrumental conditions.

Normally, X-ray analysis of samples is restricted to samples which are flat and placed at known angles to the electron beam. In the analysis of powder particles or rough bulk samples where the surface character is of interest, conventional sample preparation, involving, for example, cutting and polishing will destroy the surface property. However, X-rays emitted from such irregularly shaped surfaces are influenced by the "geometry" of the surface leading to effects that are dependent on mass, absorption and fluorescence. Mass effects produce a reduction in measured X-ray intensity, due to electrons escaping from the side of a specimen surface. Absorption effects are due to differences in the absorption pathlength of X-rays produced from within the sample compared with those from the surface. The characteristic X-ray intensity emitted by an element may also be enhanced by secondary X-ray fluorescence produced by excitation of another element, within the bulk sample. These secondary radiations are usually significant when heavy elements are present in a matrix of otherwise light elements. Nevertheless, for rough bulk specimens the dimensions of the sample are usually large enough to absorb any secondary emissions and, in this case, fluorescence effects are not generally significant. Various methods exist to compensate for these effects but the peak-to-background ratio of Stratham (1979) and Small et al (1979; 1980) have shown the most promise (Goldstein et al, 1981). Both the characteristic and background X-rays, though produced by different effects are produced within nearly the same volume (mass effect) and, further, show similar absorption effects. Therefore, the background intensity can be used as an internal standard. The ratio of the net characteristic elemental intensity to the total background signal, that is the peak-to-background

ratio,p/b, has been used successfully for the analysis of rough particles such as pyrite, talc and zinc sulphide.

Two types of instruments are available for detection of X-rays emitted, the energy dispersive spectrometer EDS, or the wavelength dispersive spectrometer WDS. In the EDS, all or most of the X-rays emitted by the dispersing system are collected by a detector and analysed in terms of the energy of the incoming X-ray photon. With the WDS system, an X-ray spectrometer consisting of an analysing crystal disperses the X-rays by diffraction in accordance with the Bragg equation. The diffracted X-rays are then collected and analysed by plotting X-ray intensity against the Bragg angle.

2.2.4.1 Powder preparation for SEM

A sample of powder or of powder mix was gently tapped down on to metal stubs previously coated with carbon dag (Polaron Equipment Ltd, Watford, U.K.). The powders were transferred when the dag had begun to dry, to avoid particles from sinking into the dag. Stubs were placed under a gold plate in a specimen chamber (Model S150B, Edwards Sputter Coater, Crawley, U.K.) and coated with gold using the sputtering technique. The coating of non-conductive particles reduces heat damage by thermal effects of the electron beam and also eliminates the build up of surface charge which can interfere with imaging and analysis. The specimen chamber was first evacuated to about 2×10^{-5} bar to dry the sample and chamber, and argon gas introduced until the pressure was stabilised at 8×10^{-5} bar. A high potential difference, 1.3-1.4 keV, was applied across the gold plate to produce a glow discharge. Under these conditions, argon atoms are ionised and strike the gold plate causing atoms of gold to be ejected which forms a uniform coat on the stub surface.

The thickness of the film formed is controlled by the magnitude of the applied voltage, discharge current ($\sim$ 10mA) and duration of the process. Five minutes coating time was found to be sufficient for a suitable conductive coat to be formed without loss in intensity of X-rays emitted from particles. The metal stubs were then held in a sample holder using screws and introduced into the specimen chamber of the scanning electron microscope through an evacuated air lock. Drying of the sample is essential since electrons produced within the electron microscope are readily scattered by water. Also, the high vacuum environment of the microscope makes the use of wet specimens difficult.

2.2.4.2 Qualitative and quantitative analysis

To explain some of the differences in dissolution profiles observed, it was necessary to obtain both a visual, qualitative and quantitative assessment of the spatial arrangement of the particles in powder mixes which were packed into capsules. It was of particular interest to identify whether ordered units had been formed in powder mixes. Formulations containing 250-355μm size diluent were examined. Phenytoin sodium and magnesium stearate were detected by emissions from Na and Mg ions respectively. Diluent particles were easily identified by size. Theoretically the concentrations by weight of Na^+ and Mg^{2+} being detected in phenytoin sodium and magnesium stearate powders were 8.02 and 4.11% respectively.

Initially, qualitative analysis of the particles within the powder mix was undertaken using a WDS system (733 Superprobe, Jeol, Tokyo, Japan) because of the low elemental concentrations involved. The operating conditions of the microscope were based on a working

distance of 11mm, an accelerating voltage of 15kV, a beam current of 0.5×10^{-7}A and a probe size on the surface of the diluent equivalent to 125μm^2. The method though offering good resolution and separation of characteristic X-rays from background radiation, was very tedious and slow; typical analysis time for a single probe area was 15-30 minutes. The lactose surfaces exposed to high beam currents for such long counting times tended to get damaged due to overheating. Also in a WDS system, the spectrometers are positioned at various angles around the sample; X-rays emitted may therefore travel different absorption paths from a rough surface to the detector and the measurements are particularly sensitive to the alignment of a particle in relation to the detector position. Therefore an energy dispersive spectrometer (EDAX, EDAX Int., Prairie View, U.S.A.) was used for quantitative analysis, although the capability for detection of elements was much lower than when using the WDS. The operating conditions of the electron microscope (Jeol 35C, Jeol, Tokyo, Japan) involved a working distance of 39mm, an accelerating voltage of 10kV, a beam current of 7×10^{-10}A and a probe area on the specimen surface of 125μm^2. The electron beam was focussed at random on a diluent surface and the X-ray count collected for 50 seconds.

The number of X-rays which are produced and which interact with radiation detectors in a given time are random but have a fixed mean value. A plot of number of X-ray counts against energy ideally conforms to a normal (Gaussian) distribution. If N counts are recorded for a particular area, the standard deviation, σ_c, is given by the square root of N and the standard error, SE, by $\frac{\sigma_c}{N}$. Thus the higher the count obtained the lower the error margin. This can normally be achieved by using long counting times whenever possible. Lactose

surfaces were damaged by the electron beam as mentioned above, and loosely held adherent particles shifted as a result of the energy imparted by the electron beam. Furthermore, instrumental drift occurs on long exposure times, thus a compromise of 50 seconds had to be used.

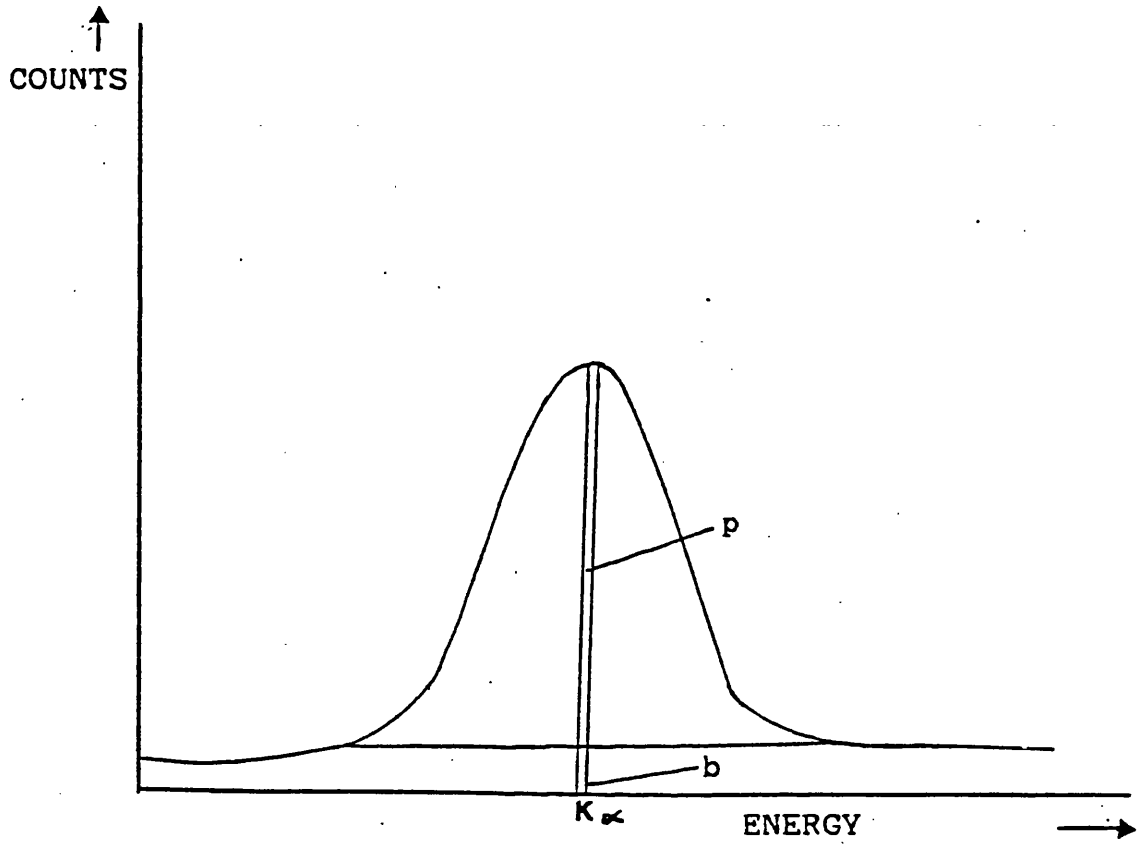
Peak-to-background ratios were calculated for Na^+ and Mg^{2+} by a built in microcomputer after background levels had been fitted. The ratio p/b was calculated as the ratio of the number of peak characteristic counts to the background count on the $K\alpha$ energy channel (Fig. 2.8). Twenty probe areas were characterised for each powder mix. The p/b ratio gives a measure of drug and lubricant concentration on the surface of the diluent particles. Results were assessed by analysis of variance.

The p/b analytical technique was used to characterise samples from the various series of powder mixing experiments in order to obtain the following information:

1. The effect of increasing concentrations of phenytoin sodium (0, 5, 10, 20 and 30%) on the amount of drug adhering to the diluent D_1, D_2 or D_4.
2. The effect of increasing concentrations of magnesium stearate (0, 0.5, 1.0, 2.5, 5 and 10%) on the amount of lubricant adhering to the diluent D_1, D_2 or D_4.
3. The effect of adding increasing amounts of magnesium stearate (0.5, 1.0, 2.5 and 5% $^w/_w$) to a two-component mix containing 95% diluent, following a P-D-L mixing sequence, on the amount of drug and lubricant adhering on the diluent D_1, D_2 or D_4.
4. The effect of adding 0.5% magnesium stearate to binary mixes of drug and lactose D_1 or D_2 containing different amounts of diluent. The diluent concentrations were 80, 90 and 95% $^w/_w$.

5. The effect of mixing sequence D-L-P, P-L-D and P-D-L (defined in Section 2.2.3.4, page 98) on the amount of drug and lubricant adhering to the diluent surface. Lubricant and diluent concentrations were 0.5 and 95% $^{w}/_{w}$ respectively.

Fig. 2.7 Definition of peak-to-background ratio, p/b, used in the EDAX system. p, is the net characteristic X-ray count on the Kα energy line and b, the background count. The Kα energy lines for Na^{+} and Mg^{2+} are 1.041 and 1.253 keV respectively



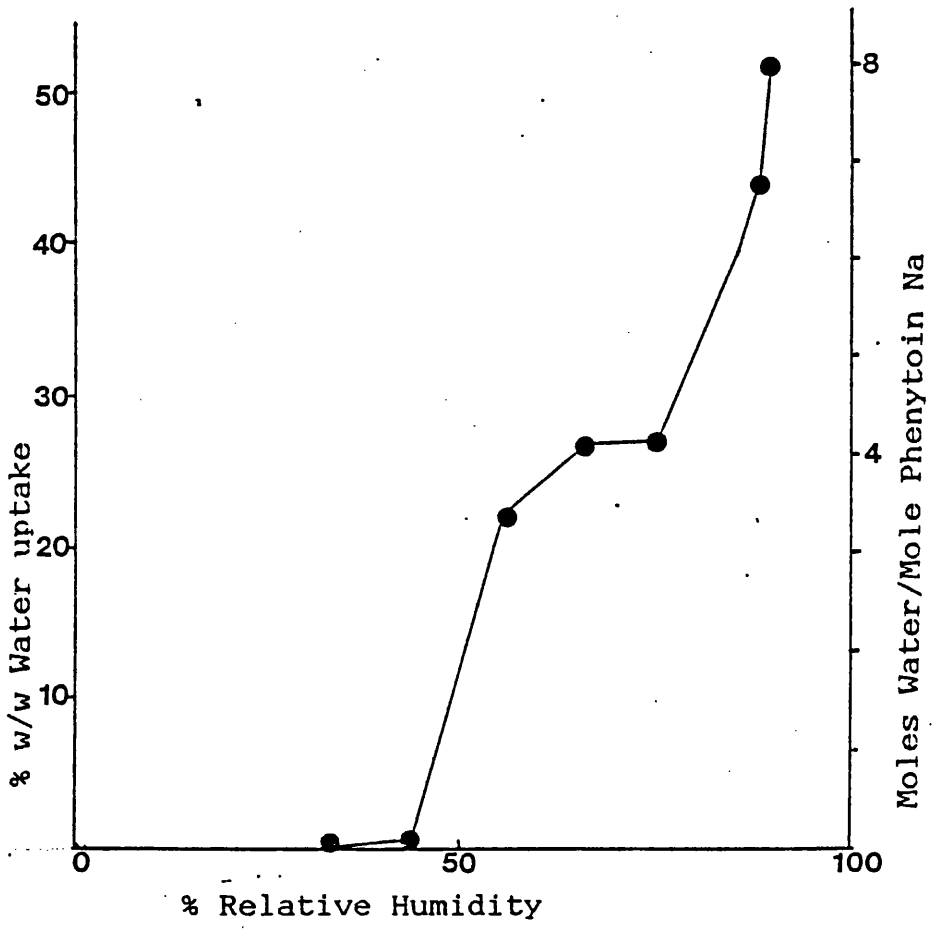
3. RESULTS AND DISCUSSION

3.1 PHENYTOIN SODIUM - WATER INTERACTION

3.1.1 Hygroscopicity

Figure 3.1 shows the moisture sorption isotherm for phenytoin sodium. The percentage of water absorbed increased with increasing RH passing through a plateau at about 55-75% RH indicating the formation of a stable hydrate with the water content corresponding to 4 moles of water per mole of phenytoin sodium. Ishiguro et al (1958) have reported the existence of mono-, tetra-, hepta-, octa-, and hendecahydrates of phenytoin sodium, but in this work only the tetrahydrate was distinguishable in terms of the sorption isotherm.

Fig. 3.1 Moisture sorption isotherm for phenytoin sodium



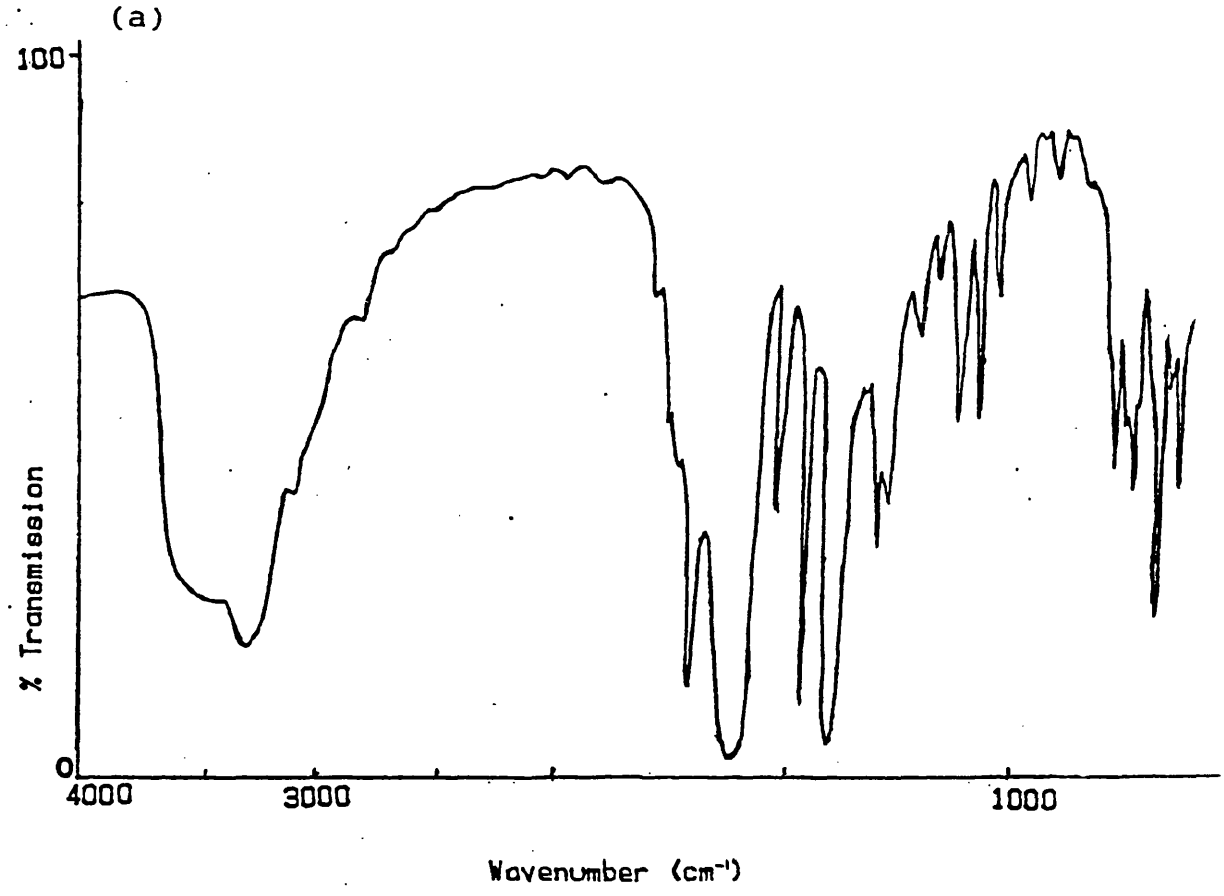
3.1.2 Infra-Red spectra

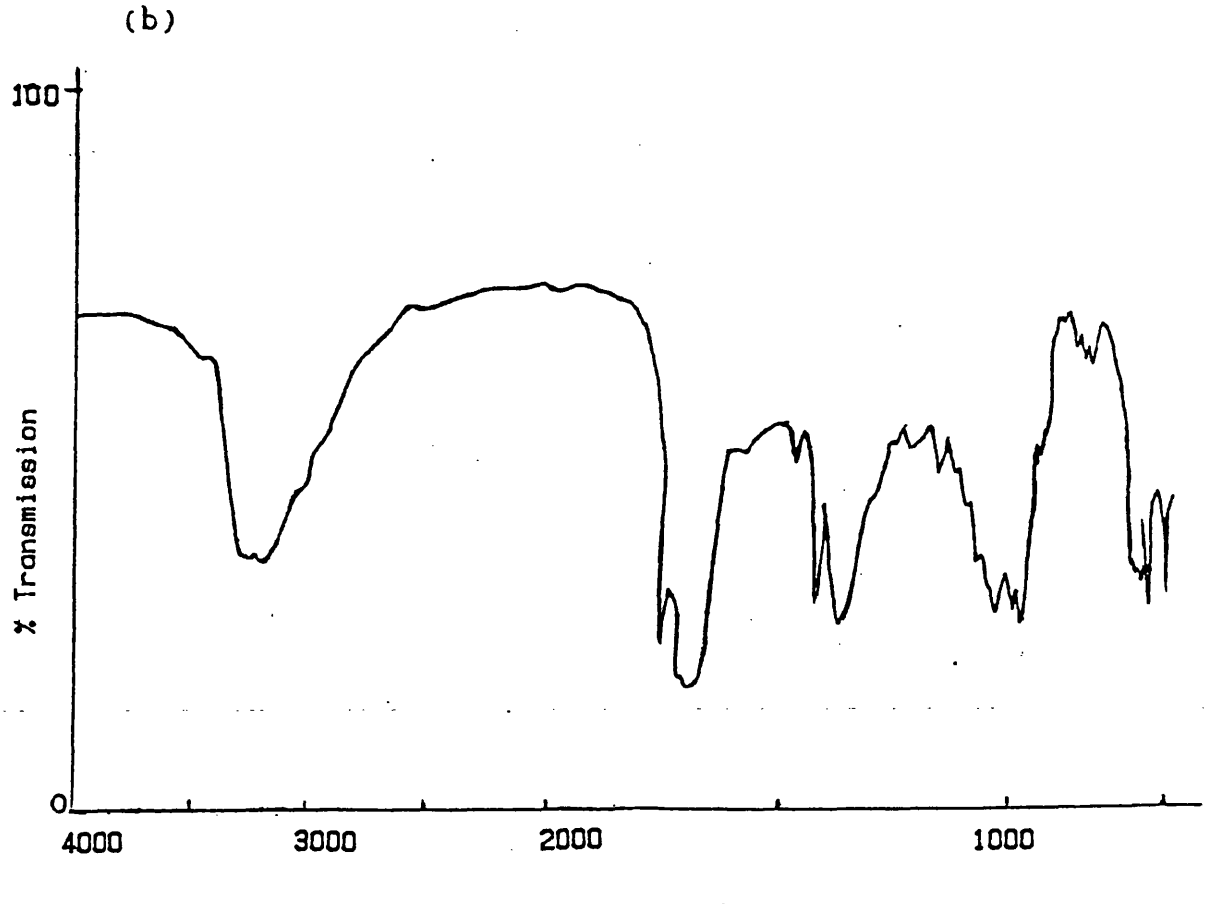
A typical IR spectrum for phenytoin sodium when stored under 75% RH and having sorbed 4 moles of moisture is shown in Fig. 3.2a. The broad band at 3600-3200 cm^{-1} is due to the hydroxyl group ν_{OH} and the amido group ν_{NH}. The presence of the hydroxyl peak at 3600cm^{-1} indicates that water molecules are probably bound and not extraneous to the lattice structure. The band at 1600cm^{-1} is due to the carbonyl group $\nu_{C=O}$ at the 4 carbonyl position (refer Fig. 1.1b) and at 1610cm^{-1} to the vibration of the N=C-O group. Peaks appearing at 1770, 1750 and 1720cm^{-1} indicate that phenytoin has been precipitated due to reaction either with water molecules or atmospheric carbon dioxide. Fig. 3.2b shows the IR spectrum for dried phenytoin which exhibits typical carbonyl vibrations at the 1770cm^{-1} and also at 1750 and 1715cm^{-1}. Usually in solid state spectra, bound water molecules may also show weak absorption within the range 1640 to 1615cm^{-1}. However, for hydrated phenytoin sodium samples due to the two strong peaks in this region, this peak could not be detected.

3.1.3 Differential Scanning Calorimetry

The DSC curves for phenytoin sodium hydrates are shown in Fig. 3.3. For powders which had sorbed 23-26% water equivalent to approximately 4 moles of water per mole of phenytoin sodium, three broad endothermic peaks were observed from 50-93°C. Peak temperatures were observed at 62, 83 and 93°C (Fig. 3.3a). The first peak is probably due to the conversion of a crystal hydrate to a lower hydrate and the formation of a solution saturated with this new phase. With

Fig. 3.2 Infra-red spectra of
(a) Phenytoin sodium stored under 75% RH
(b) Phenytoin (anhydrous)





further increase in temperature, the lower hydrate melts at 83°C to an anhydrous form and a solution from which water is lost at 93°C. Ishiguro et al (1958) used a differential tensiometer operated at different temperatures to measure the dissociation and vapour pressures of phenytoin sodium hydrates; the mono-, tetra-, hepta-, octa- and hendecahydrate were found. Transition temperatures for the hendeca- to octahydrate, octa- to heptahydrate and hept- to tetrahydrate were reported at 37.6, 45.2 and 51.3°C respectively. The peak temperature at 62°C (Fig. 3.3a) therefore indicates a transition of the tetra- to monohydrate and the peak at 83°C, the conversion of the monohydrate to the anhydrous form. Free moisture evaporates at 93°C.

For samples containing 28-40% $^{w}/_{w}$ water, a typical DSC curve obtained is shown in Fig. 3.3b. A sharp endothermic peak from 45 to 52°C with peak temperature at 49°C and two broad peaks from 58 to 80°C and 80 to 95°C were observed. Thus although the moisture sorption curve (Fig. 3.1) does not show the formation of stable hydrates within this region, DSC curves do provide such evidence. Peak temperature at 49°C is probably due to the conversion of the hepta- to tetrahydrate. The broad endotherm shown at 58 to 80°C appears to be due to two unresolved peaks and is probably a combination of endothermic transitions of tetra- to monohydrate and monohydrate to anhydrous state.

For samples containing 53% $^{w}/_{w}$ water, the DSC curve obtained is shown in Fig. 3.3c. Water content indicates that the sample obtained might be the octahydrate, however the sharp endothermic peak obtained at 31.5°C indicates that the hendecahydrate is also present. Four

other broad endotherms occurred between 40-95°C with peak temperatures at 47, 61, 74 and 86°C. Dehydration therefore appears to follow the sequence hendeca- to heptahydrate, monohydrate to anhydrous form with intermediate formation of the tetrahydrate. It is possible that the shoulder obtained at 49°C is due to an unresolved peak although the collapse of the powder sample in the aluminium pan may cause a similar effect.

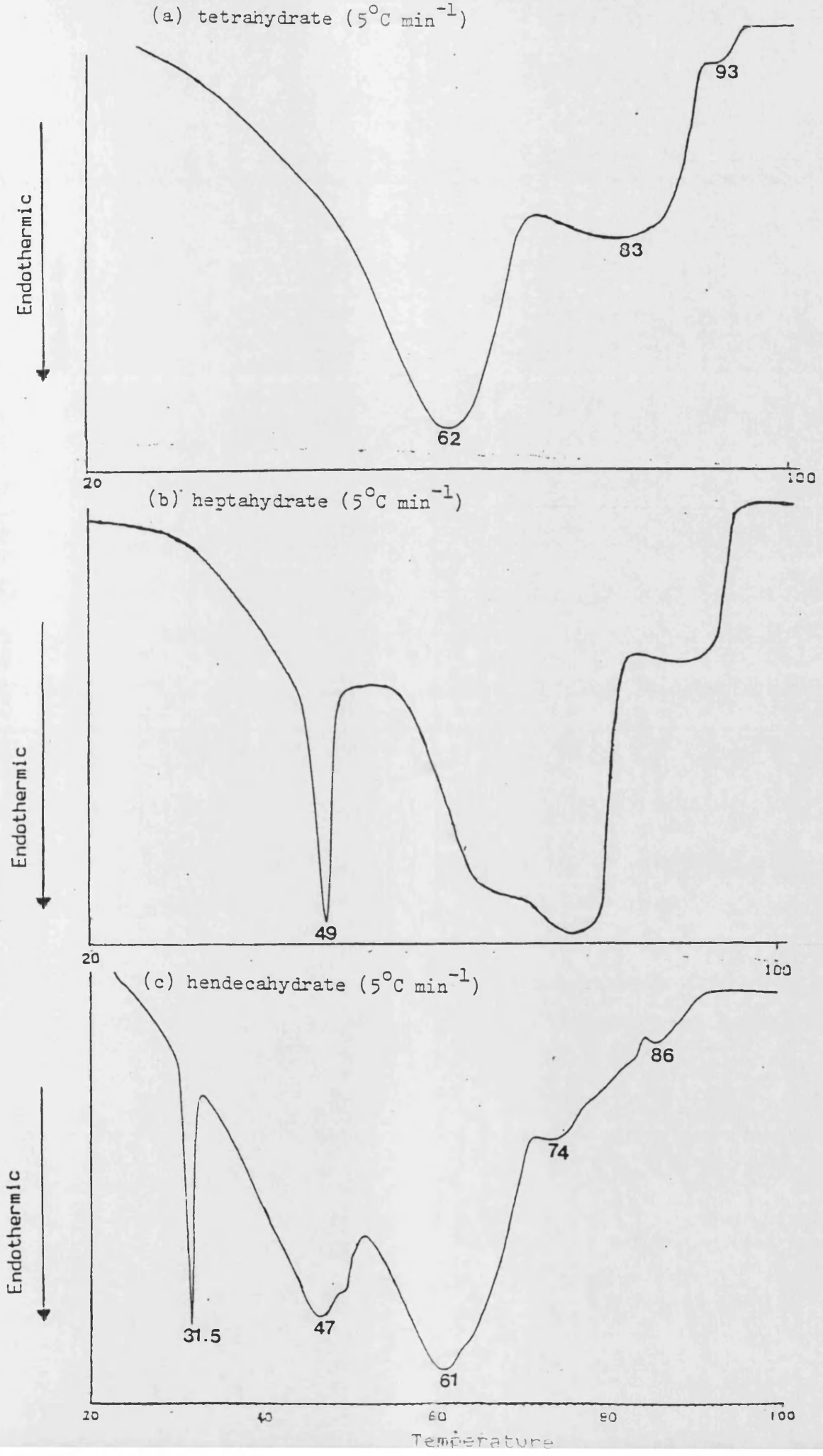
Fig. 3.3d shows the DSC curve for phenytoin sodium sample as received from the manufacturer containing 1.4% $^{w}/_{w}$ of water. (Table 2.6) Three broad endotherms are observed between 30 and 95°C indicating that hydrates of phenytoin sodium were present in the sample. The endothermic transition at 35°C indicates that the hendecahydrate was present. Partial hydration of the phenytoin sodium could well have occurred during storage and transport since the drug is hygroscopic. The manufacturers do not therefore claim that the drug is anhydrous.

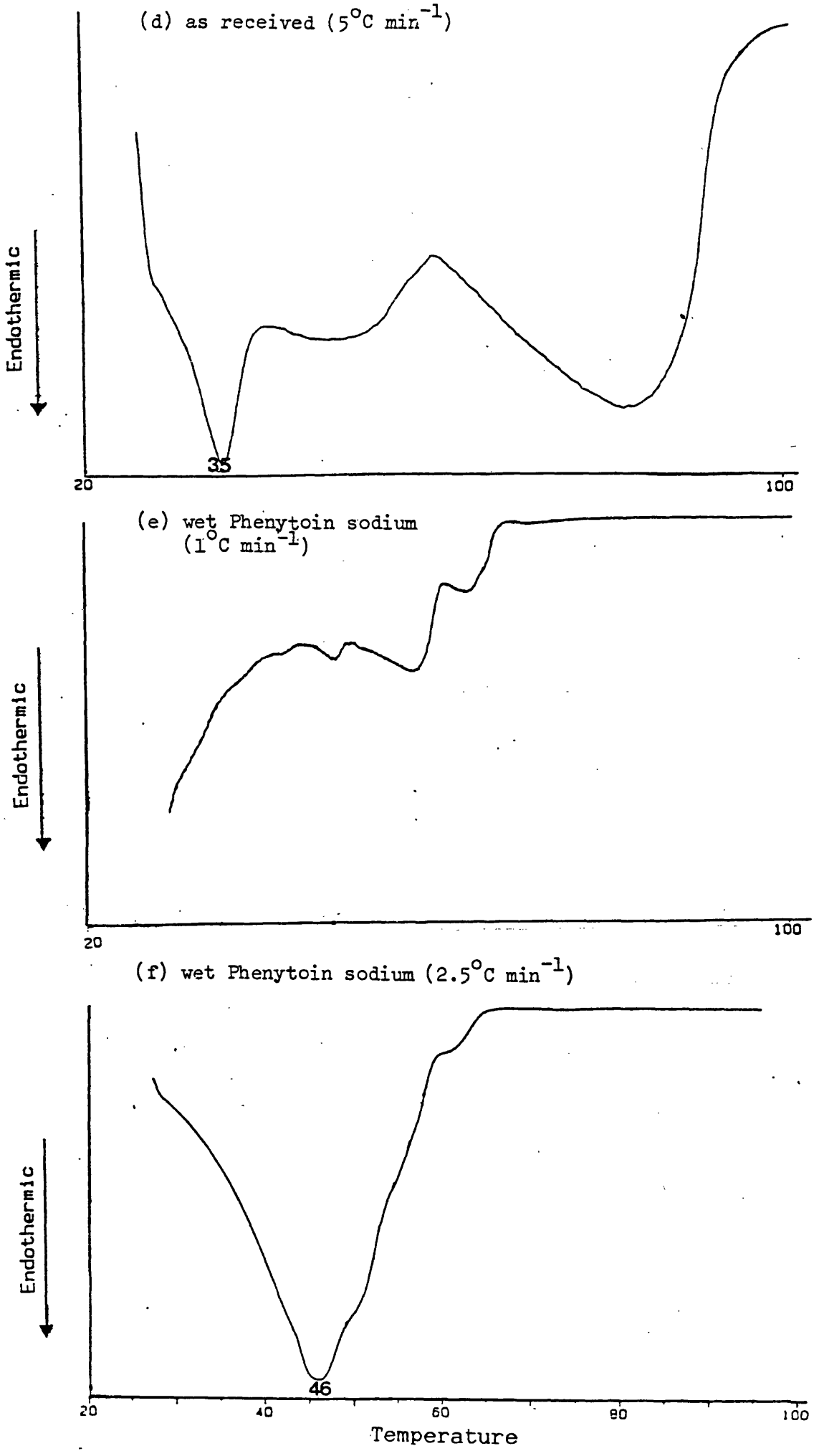
When phenytoin sodium had been saturated with water the DSC curves obtained varied with heating rate. At a very low heating rate of 1°C/min (Fig. 3.3e) the dehydration of the lower hydrates was shown more clearly by distinct peaks than in the case of the higher hydrates. When the heating rate was increased to 2.5 and 5°C/min (Fig. 3.3g and f) dehydration of the higher hydrate was now more distinct. Dehydration of wet phenytoin samples probably occurs through dehydration of the hendecahydrate with the formation of lower hydrates.

3.1.4 X-ray powder diffraction

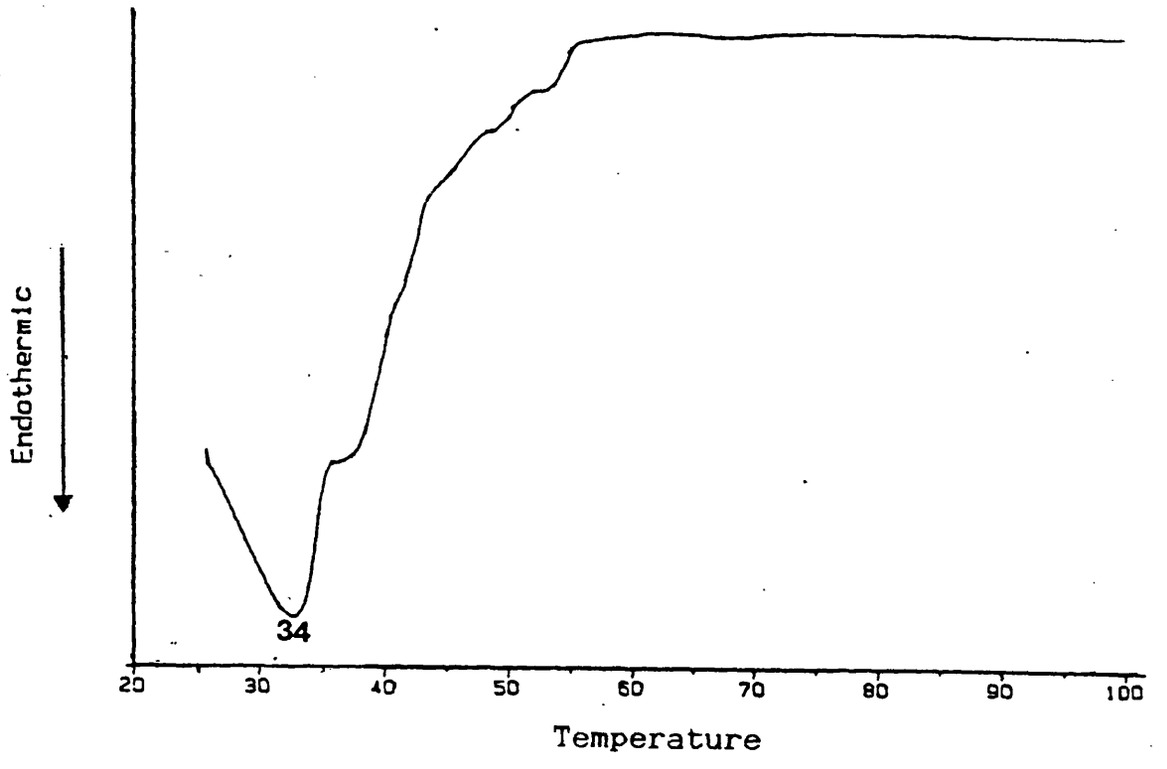
The X-ray powder diffraction pattern for phenytoin sodium showing the changes in crystalline structure associated with an increase in water content are shown in Fig. 3.4. There is a progressive

Fig. 3.3 DSC curves for hydrates of Phenytoin sodium




(d) as received (5°C min⁻¹)
Endothermic
35
20
100
(e) wet Phenytoin sodium (1°C min⁻¹)
Endothermic
20
100
(f) wet Phenytoin sodium (2.5°C min⁻¹)
Endothermic
46
20
40
60
80
100
Temperature

(g) wet Phenytoin sodium ($5^{\circ}C\ min^{-1}$)

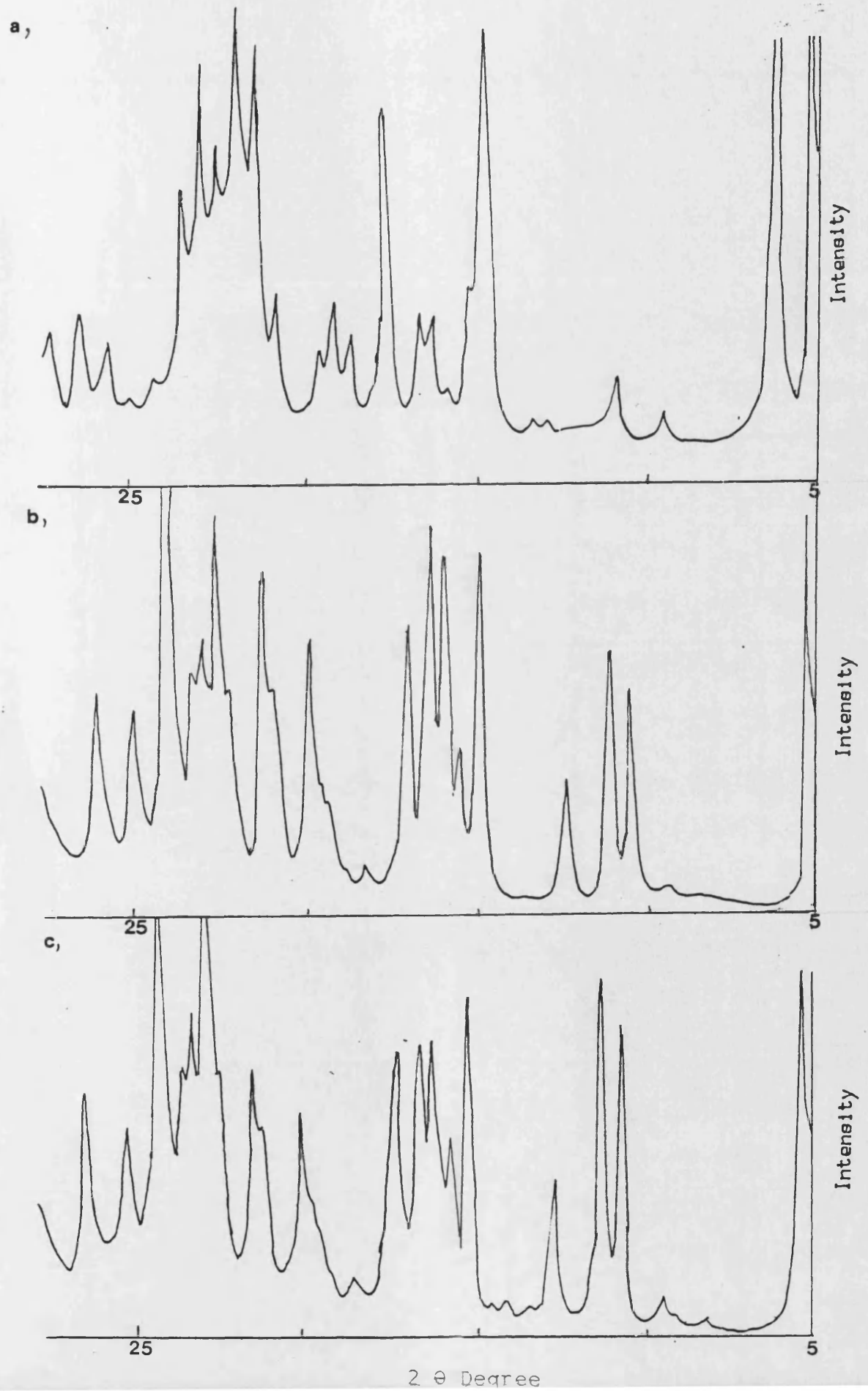


decrease in intensity of most peaks with increasing water content, suggesting a decrease in crystallinity. A typical X-ray diffraction pattern for samples stored at 55, 67 and 75% RH and containing 20-26% $^{w}/_{w}$ water is shown in Fig. 3.4b. There are distinct differences in this pattern as compared to Fig. 3.4a for the dried phenytoin sodium. The most obvious differences occurred in the range 5-15° on the abscissa (2θ degrees). This pattern corresponds to the tetrahydrate as discussed under hygroscopicity (Section 3.1.1) and DSC (Section 3.1.3). The diffraction pattern observed in this region was unchanged when the sample was heated to 50 ± 0.5°C supporting the evidence obtained using DSC which showed that the transition to the monohydrate occurred around 60°C.

For phenytoin sodium containing 28% $^{w}/_{w}$ water, the diffraction pattern (Fig. 3.4c) was similar to the tetrahydrate (Fig. 3.4b) except that peaks occurred within the region 12-15° on the abscissa. This evidence of crystallographic change is probably due to partial conversion to a higher hydrate. When the water content increased to 30% $^{w}/_{w}$ (Fig. 3.4d), the peaks in the 2θ degree range of 12-15 was now more pronounced whilst the peak at 2θ equal to 5.2 degrees was lost or shifted to a lower angle. Also extra peaks appeared within the range 2θ equal to 24-28°.

When samples contained 40% water, the diffraction pattern was markedly changed as shown in Fig. 3.4e; this is probably due to the formation of the heptahydrate as intepreted from the DSC curves. X-ray diffraction pattern observed for saturated powder samples at room temperature are shown in Fig. 3.4f corresponding to the hendecahydrate.

Fig. 3.4 X-ray diffraction patterns for phenytoin sodium showing changes in crystalline structure on increase in water content. (a) dried sample (b) 20-26% $^{w}/_{w}$ (c) 28% $^{w}/_{w}$ (d) 30% $^{w}/_{w}$ (e) 40% $^{w}/_{w}$ (f) thoroughly wet



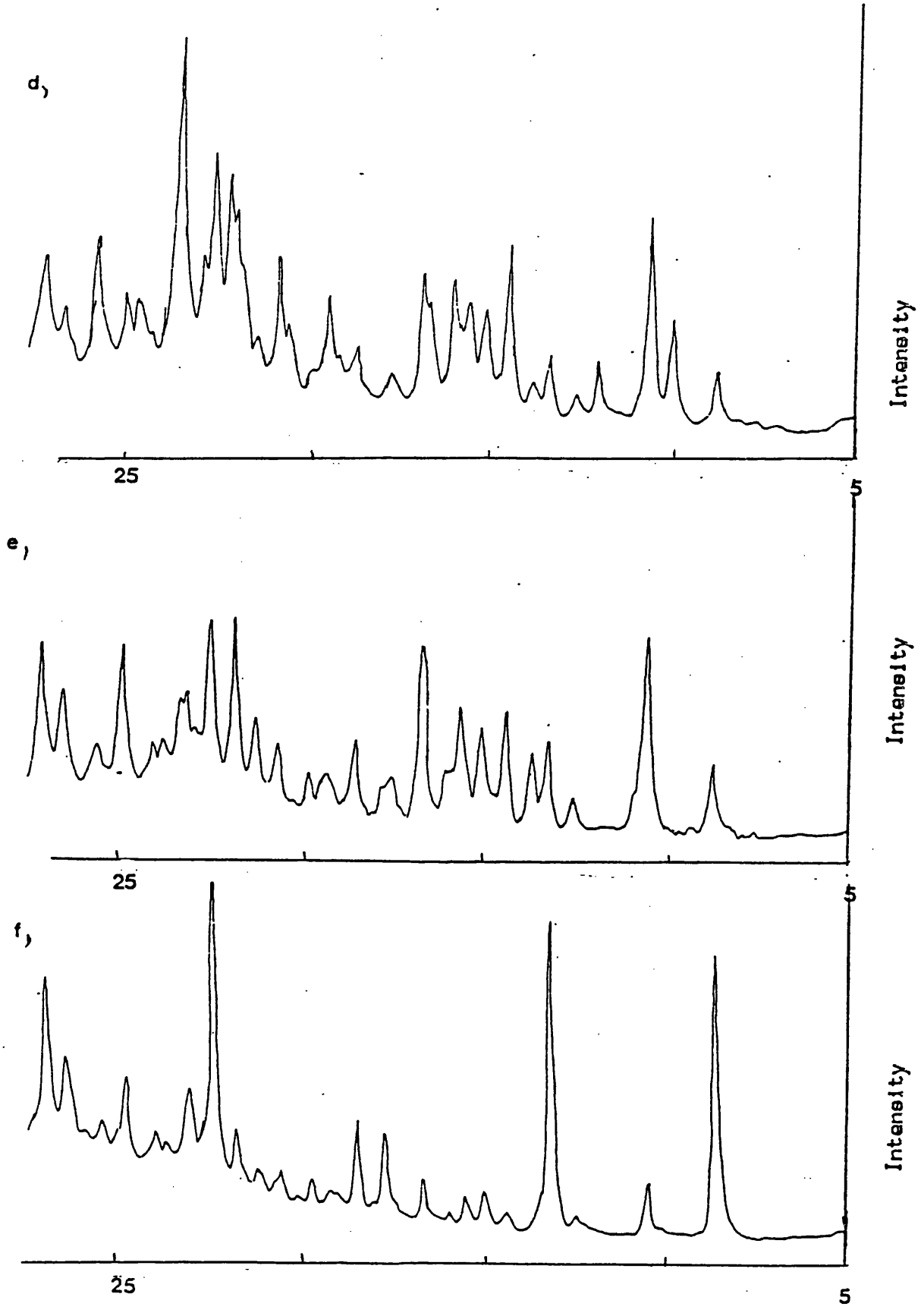

d)
Intensity
25
5
e)
Intensity
25
5
f)
Intensity
25
5
2 θ Degree

Table 3.1 Powder diffraction data for phenytoin, phenytoin sodium and its hydrates

2θ degrees	Phenytoin (plates)		Phenytoin sodium (anhydrous)		Phenytoin sodium $\cdot 4H_2O$		Phenytoin sodium $\cdot 7H_2O$		Phenytoin sodium (wet)	
	d, Å	I/I_o	d, Å	I/I_o	d, Å	I/I_o	d, Å	I/I_o	d, Å	I/I_o
5-10			16.85	94	17.01	50				
			14.27	100						
	10.31	12								
							10.02	31	9.91	59
			9.34	6						
10-15					8.54	38				
			8.19	9			8.19	86	8.23	9
					8.08	44	8.08	15		
	7.87	20								
					7.18	23				
							7.01	14		
	6.91	20								
			6.85	2						
			6.65	3			6.65	38	6.60	70
							6.44	32		
							6.12	51		
			6.00	77	6.02	58				
15-20			5.86	23	5.77	25	5.84	31	5.84	9
			5.63	3	5.63	58	5.65	54	5.65	6
							5.52	17		
	5.43	41	5.44	15	5.46	64	5.49	17		
			5.33							
					5.27	56	5.27	75	5.26	9
	5.21	32								
			5.04	53			5.06	15		
	4.96	21			4.95	4	4.96	12	4.95	20
			4.76	14	4.77	3	4.78	31	4.75	31
	4.66	7	4.65	20	4.69	11				
			4.58	10	4.62	17	4.60	15	4.57	6

Table 3.1 continued

2θ degrees	Phenytoin (plates)		Phenytoin sodium (anhydrous)		Phenytoin sodium $4H_2O$		Phenytoin sodium $7H_2O$		Phenytoin sodium (wet)	
	d, Å	I/I_o	d, Å	I/I_o	d, Å	I/I_o	d, Å	I/I_o	d, Å	I/I_o
20-25			4.47	23	4.51	39	4.48	15		
	4.44	43								
			4.28	64	4.30	33	4.30	28	4.30	11
			4.17	69	4.23	50	4.19	28	4.18	3
	4.06	30			4.06	32	4.09	69	4.09	9
	4.00	22	3.98	46	4.00	64	3.98	62		
					3.93	39	3.91	15	3.95	100
			3.90	54	3.88	31	3.88	23		
			3.83	37			3.85	20	3.86	30
					3.79	100	3.79	15	3.77	4
			3.70	6			3.73	15	3.72	11
25-30			3.59	2	3.65	25	3.62	61	3.61	21
	3.54	39	3.51	11	3.49	29	3.52	15		
	3.41	10	3.41	17			3.41	38	3.40	40
	3.33	13	3.32	15	3.31	13	3.34	60	3.33	50
			3.27	11			3.25	14	3.25	12
			3.21	11	3.18	22	3.18	5		
	3.16	5	3.14	2	3.16	17				
	3.11	3			3.09	31	3.11	14		

The lattice d-spacings calculated from the Bragg equation (Equation 2.2, page 86) and the relative intensities are presented in Table 3.1. The d-spacings correspond to distances within planes in the lattice structure and the intensity of the reflected beam is proportional to the product of the intensity of the incident beam and the concentration or density of electrons in the plane. Lattice d-spacings for phenytoin which possessed a plate-like habit have been included in Table 3.1 for comparison, and also to show possible lattice d-spacings in the samples of phenytoin sodium and its hydrates which may be due to the presence of the free acid. Generally most of the peaks appeared to shift slightly or sometimes disappeared on hydration. However, peaks occurring at 5.86, 5.63, 4.58, 4.76, 4.28, 4.17, 3.59 and 3.32Å appeared in all the hydrates and anhydrous form studied. These spacings refer to lattice distances which are unchanged during hydration. Overall, although differences in X-ray diffraction data are observed, most of the differences are only slight. The most distinct differences occurred in the longer d-spaces. It is possible that on hydration water molecules are incorporated into holes or between layers within the lattice structure causing slight distortions in bond lengths.

3.1.5 Swelling capacity and swelling forces

Compacted beds of phenytoin sodium particles swell on contact with water. Fig. 3.5 shows a plot of swelling capacity (Equation 2.3, page 88) versus porosity of the powder bed. These results indicate that there is a significant inverse correlation between swelling capacity and porosity within the powder bed in the region 0.80 to 0.55.

With an increase in packing fraction equivalent to a decrease in porosity, the swelling capacity was increased. When the force exerted during swelling was measured it was observed that for powder beds of porosities between about 0.80 to 0.65, as the porosity decreased there was a linear increase in the swelling force (Fig. 3.6). Swelling force appeared to approach a limiting value with further reduction in porosity.

Phenytoin sodium powder in the dry state consists of aggregates and agglomerates of fine needle-like particles (Fig. 2.1a). It is also hygroscopic (Section 3.1.1). Thus, in addition to the effect of the fine particle size which will cause considerable particle interaction due to London-Van der Waals forces, it is to be expected that surface moisture and solid bridging will also contribute considerably to cohesive bonding between powder particles. The hydrophilic nature of the powder allows particles to be easily wetted by aqueous fluid. Examination of wet powder samples (Fig. 3.7) shows powder particles to be well dispersed yet form a continuous network. These particles are the hendecahydrate and are needle-like in shape.

When certain powders in the form of particle aggregates and agglomerates are dispersed in an aqueous medium, the liquid first penetrates into channels within the agglomerates. This causes expulsion of air and provides excess pressure which brings about the dispersion of particles (Heertjes and Witvoet, 1970). Powder beds of phenytoin sodium were observed to swell to the same extent whether wetting in a desicator under vacuum or at ambient pressure, indicating that the expulsion of air did not account for the dispersion effect. Probably, the

Fig. 3.5 The influence of porosity of compacted beds of phenytoin sodium on swelling capacity

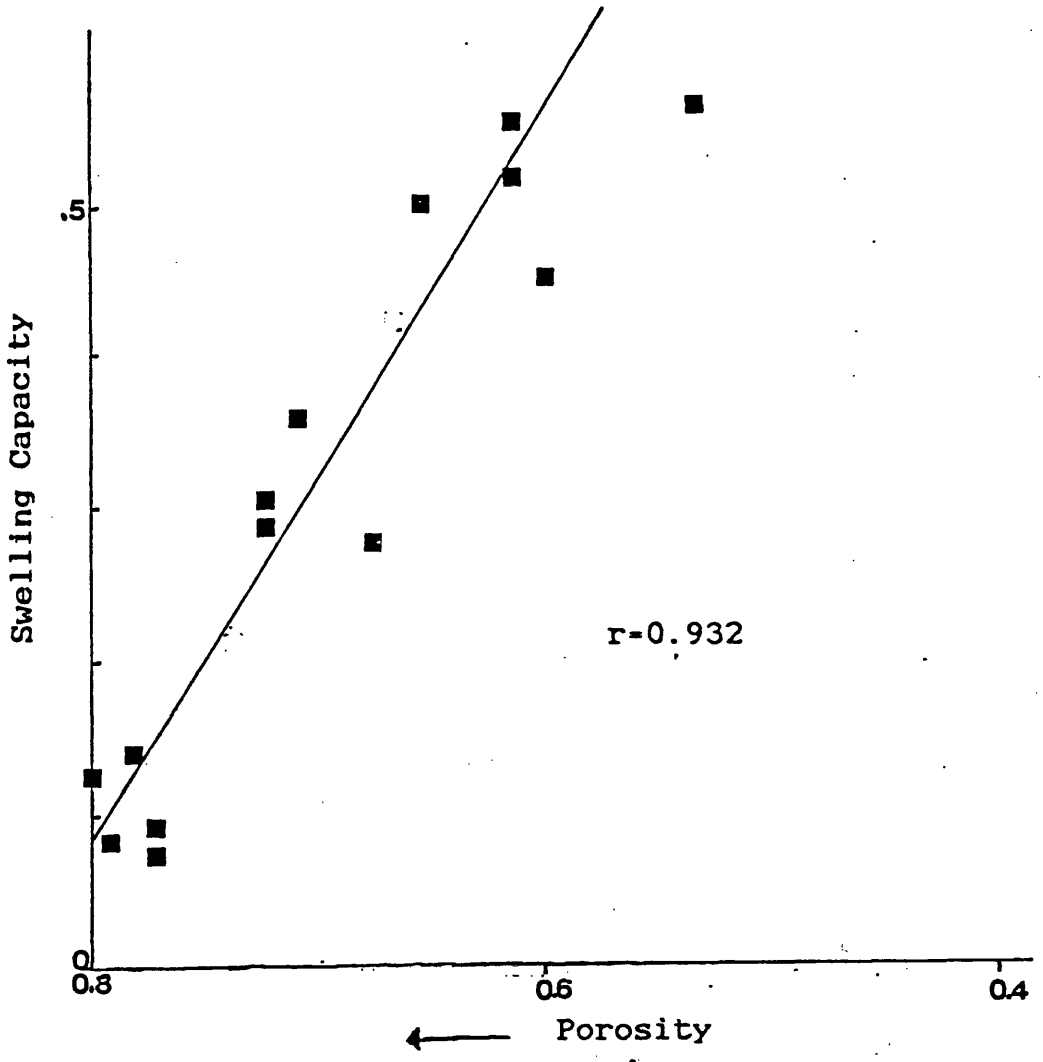


Fig. 3.6 The influence of porosity of compacted beds of phenytoin sodium on measured swelling forces (vertical bar indicates standard deviation)

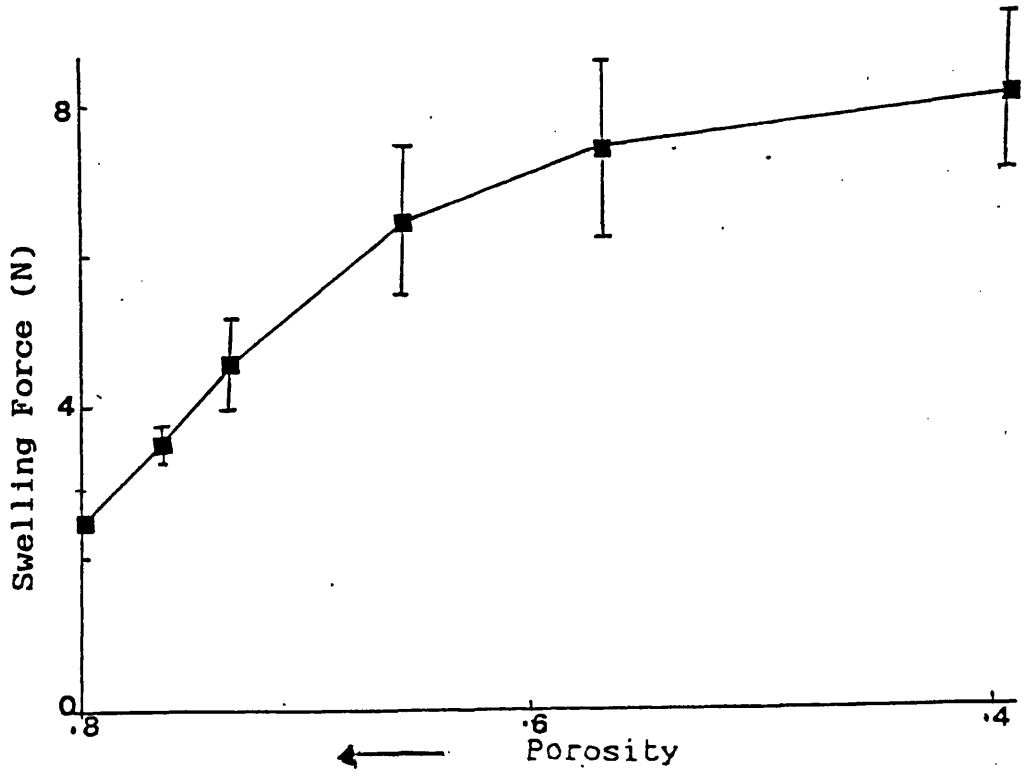
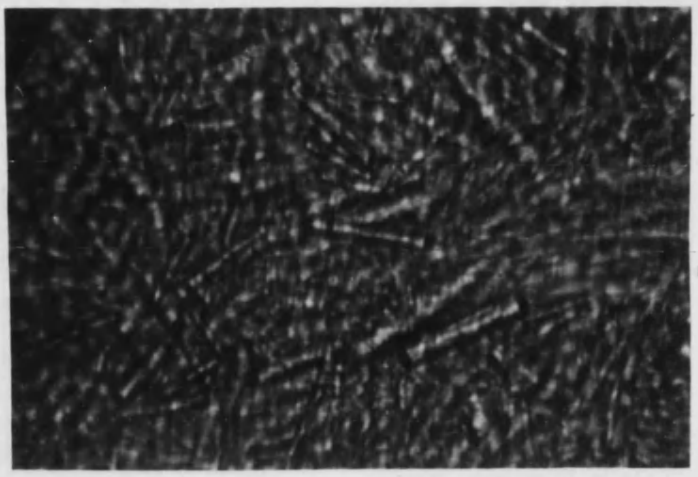


Fig 3.7 Photomicrograph of wet Phenytoin sodium particles.



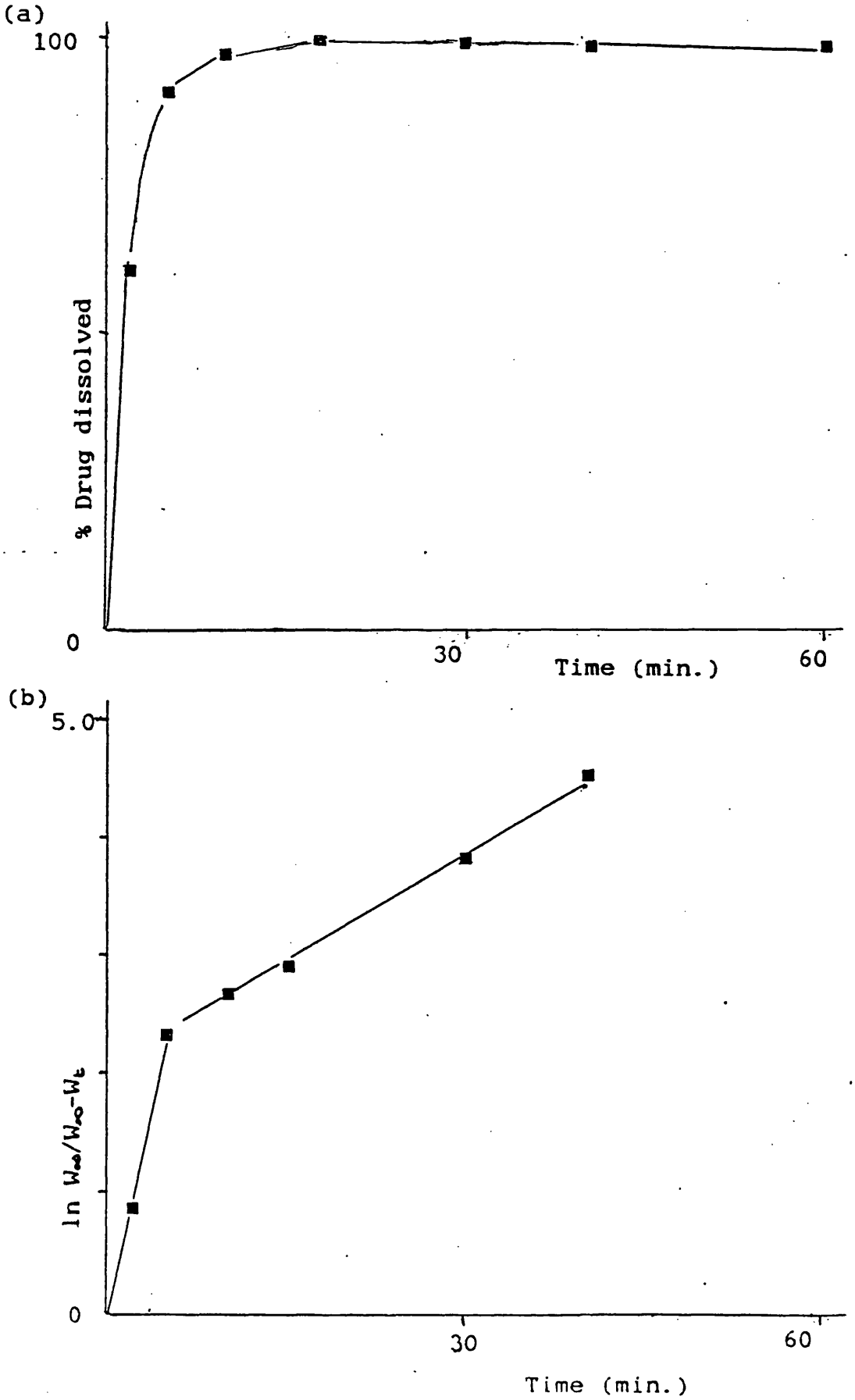
hydration of particles to hendecahydrate causes particles to experience repulsive hydration forces in the wet state and this would account for the observed dispersion and expansion of the powder bed. It is also likely that incorporation of water molecules into the lattice structure of phenytoin sodium crystals causes lengthening of bonds in the lattice along certain planes, causing particle dimensions to increase. Whatever mechanism is responsible for the observed swelling, the force of expansion or swelling is much lower in beds of high porosity due to the high interparticle voidage. As the porosities decreased, improved interparticle contact allows swelling forces to be translated through the powder bed with a resultant increase in the measured force. When the powder bed was compacted still further interparticle forces are markedly increased with a resultant decrease in surface area, thereby reducing the interaction between water and solid on wetting the solid compact. Thus the plot of swelling force versus porosity approached a limiting value at low porosities.

3.2 DISSOLUTION OF PHENYTOIN SODIUM CAPSULES: INFLUENCE OF MIXING AND FORMULATION FACTORS

The dissolution data for capsules containing phenytoin sodium were plotted according to the method of Kitazawa *et al* (1977). Typical dissolution profiles and corresponding Kitazawa plots are shown in Fig. 3.8a and b respectively. In most cases two straight regression lines were obtained from the plot, the slope of the first being designated k_i and of the second k_f. The time, t_1, at which the break in slope occurred was calculated by mathematical interpolation. Dissolution can therefore be interpreted as occurring in two stages.

Fig. 3.8 (a) Dissolution profile for 100mg phenytoin sodium contained in size 2 hard gelatin capsules.

(b) Corresponding Kitazawa plot



An initial rapid dissolution occurs in the first stage where k_i applies until time t_1, at which the rate of change in surface area available may change abruptly. In the second stage from t_1 to the completion of dissolution, k_f applies. For the capsule formulations studied, powder mixes were packed into capsule size 2 and therefore it can be assumed that for all the formulations studied the initial surface area available for dissolution was identical. Thus from the Kitazawa plots although the surface area available during dissolution may be changing continuously and regularly, such a change does not influence the dissolution rate except when it is discontinuous for example on the disintegration of the powder bed.

For the formulations studied, the dissolution rate represented by k_i, was much faster than that corresponding to k_f. However, it is expected that since dissolution rate is proportion to exposed surface area (Equation 1.6, page 14) the dissolution rate from the disintegrated dispersed particles k_f, should be higher than the initial dissolution rate, k_i. It has been suggested by Cartwright (1979) using the rotating basket that the unexpected observation ($k_i \gg k_f$) is a result of large aggregates of disintegrated tablets sinking to the bottom of the dissolution vessel. However, in these experiments the rotating paddle was used and the capsule was already positioned at the bottom of the vessel at the start of dissolution testing. It would therefore seem that this observation was associated with other factors associated with the formulation and is discussed later in Section 3.2.2.2.

3.2.1 Single - component formulation

3.2.1.1 Effect of packing and drug particle size

The dissolution of phenytoin sodium alone packed into size 2 hard gelatin capsules is fast and almost complete within 30 minutes.

Fig. 3.9 The influence of increased packing of phenytoin sodium into capsule size 2 on the dissolution rate of the drug.
▲ 50mg; ■ 100mg; ◇ 300mg; △ 400mg.

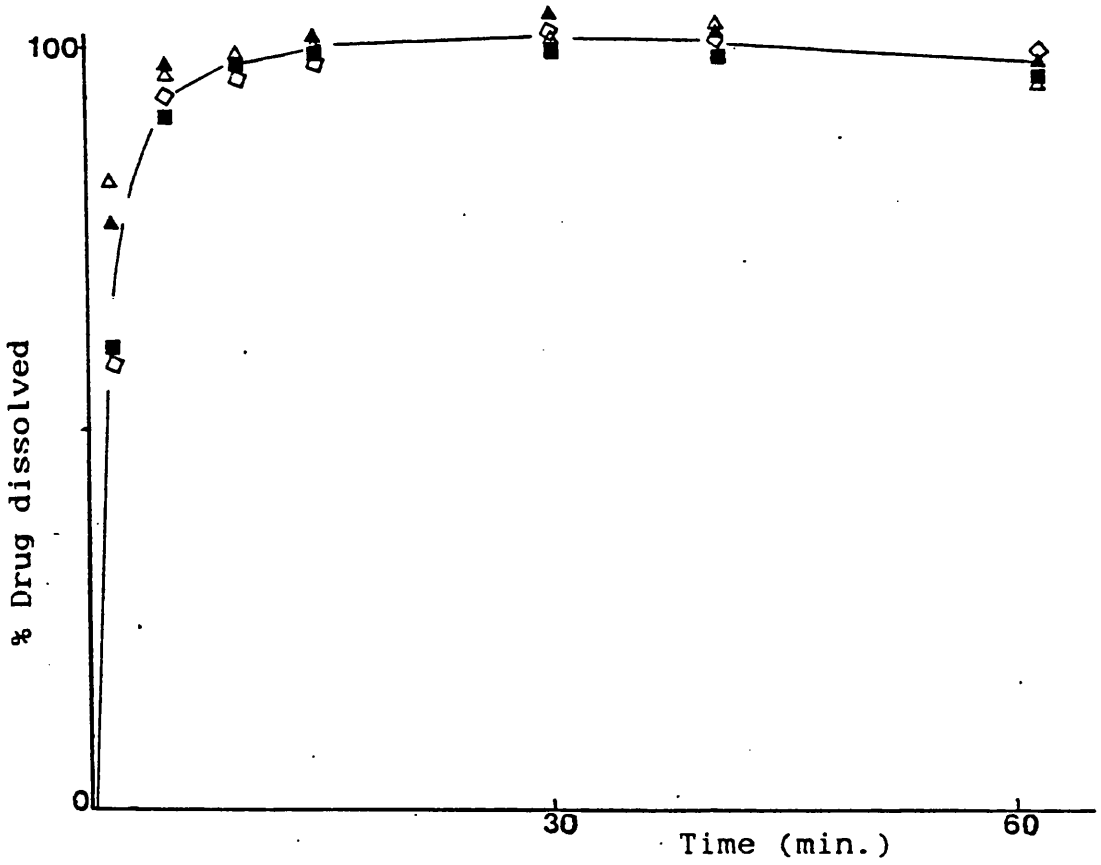
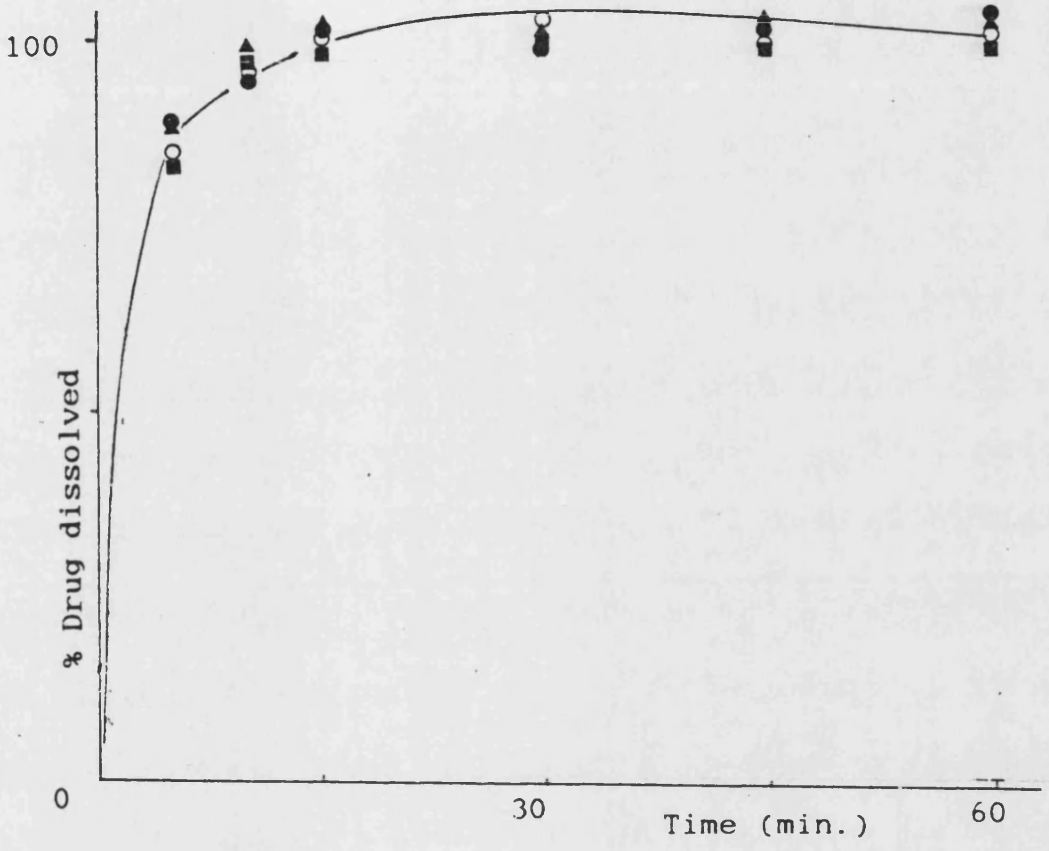


Fig. 3.10 The influence of particle size of phenytoin sodium particles on the dissolution rate of drug from capsules size 2

▲ 45 μm;● 63-90 μm;■ 90-125 μm;○ 125-180 μm.



The dissolution profile and Kitazawa plot for 100mg phenytoin sodium are shown in Fig. 3.8a and b respectively. The Kitazawa plot (Fig. 3.8b) shows fast dissolution in the k_i phase up to about 4 minutes, followed by a slower second phase. An increase in the quantity of drug in the capsule from 50mg to 400mg provided an increase in packing density corresponding to a reduction in the porosity from 0.90 to 0.42. This had no significant effect on the dissolution (Fig. 3.9). There was also no significant effect of drug particle size as shown by studies on capsules containing different sieve sized fractions ranging from particles less than 45μm to a coarse size fraction 125-180μm (Fig. 3.10).

At the start of the dissolution, there was an initial lag period of less than a minute during which the gelatin shell and powder bed became wetted. After this period the capsule was observed to burst open leading to the dispersion of capsule contents into the dissolution medium. This observation may explain why the dissolution of phenytoin sodium was found not to be influenced by porosity within the capsule.

For solid dosage formulations whose rates of dissolution are influenced by porosity, two main deductions can be made about the dissolution process. First it can be assumed that the dosage form behaves as a compacted bed and that the limiting step in the events leading to drug dissolution, is the rate of penetration or flow of fluid through pores within the powder bed. The Kozeny-Carman equation describes the relationship between liquid penetration rate, Q, and porosity, ϵ, as:

$$Q = \frac{A}{\eta S_w^2} \cdot \frac{\Delta P}{KL} \cdot \frac{\epsilon^2}{(1-\epsilon)^2} \qquad \text{Equation 3.1}$$

where A, is the cross-sectional area of the bed; ΔP, pressure difference across the powder bed; L, length of capillary through which liquid of viscosity, η, flows; S_w, the specific surface area of the powder and K, a constant.

When phenytoin sodium is wetted by the dissolution medium, a rapid chain of events involving hydration of particles and swelling of the powder bed proceeds (see Section 3.1). The hydrated particles will under laminar flow conditions be easily dispersed contributing to the large burst effect noticed. Also with a decrease in initial porosity of the powder bed there is an increase in both the swelling force and swelling capacity and this probably compensates for the effect of reduction in porosity. Another possible explanation why the dissolution of phenytoin sodium is not influenced either by powder bed porosity or drug particle size, may be related to its high aqueous solubility and hydrophilicity conferred by sodium substitution. The hydrophilic rapidly dissolving particle surfaces in the consolidated powder bed will lead to the rapid destruction of the pore structure and cause the dosage form to disintegrate. For such a system, neither the particle size and surface area of particles exposed to the dissolution medium nor the porosity of the dosage form will influence the rate of dissolution.

3.2.2 Two - component formulations

3.2.2.1 Effect of diluent type

The dissolution profiles in Figs. 3.11 and 3.12 show the effect of adding a fixed concentration of diluent, 56% $^{w}/_{w}$, to capsules containing either 92mg phenytoin or 100mg phenytoin sodium respectively. The diluents used were lactose, calcium sulphate dihydrate, calcium

Fig. 3.11 The influence of diluent type on the dissolution of drug from capsules containing 92mg phenytoin and 120mg diluent

◇ drug alone; ● lactose; ■ calcium sulphate; ▲ dibasic calcium phosphate; ▼ calcium chloride

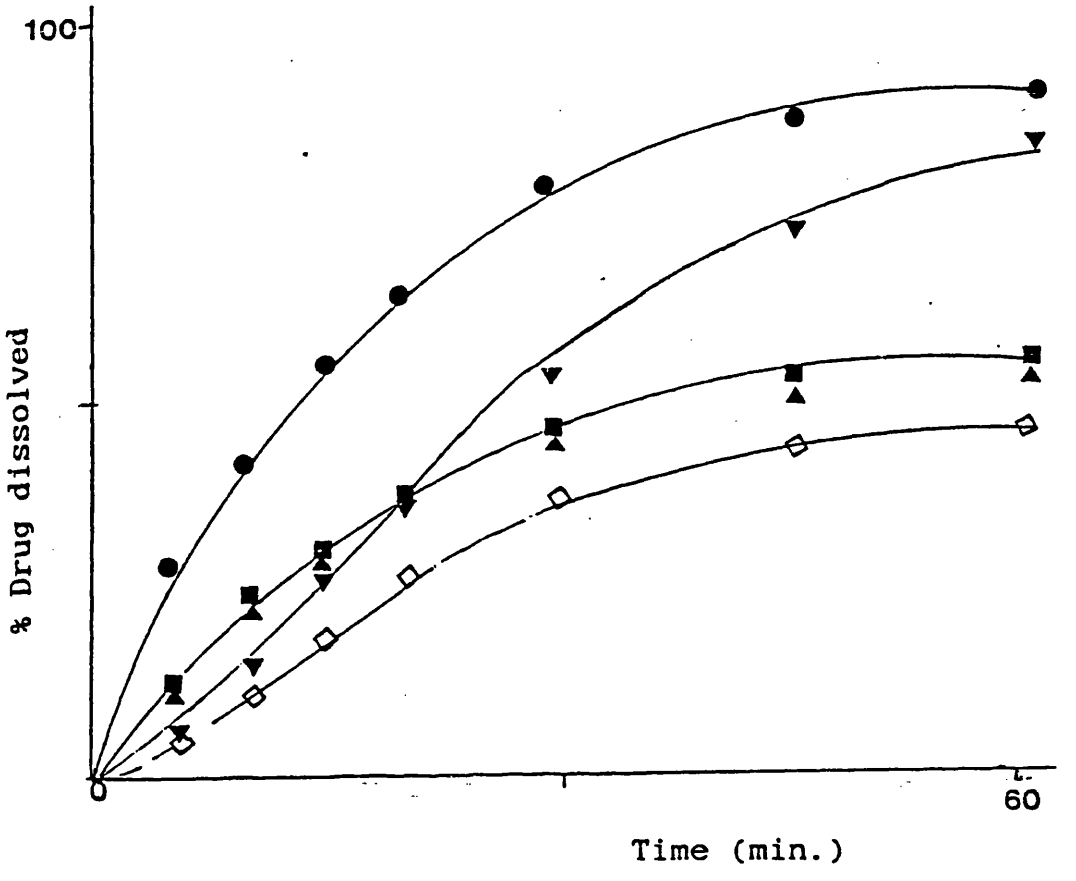
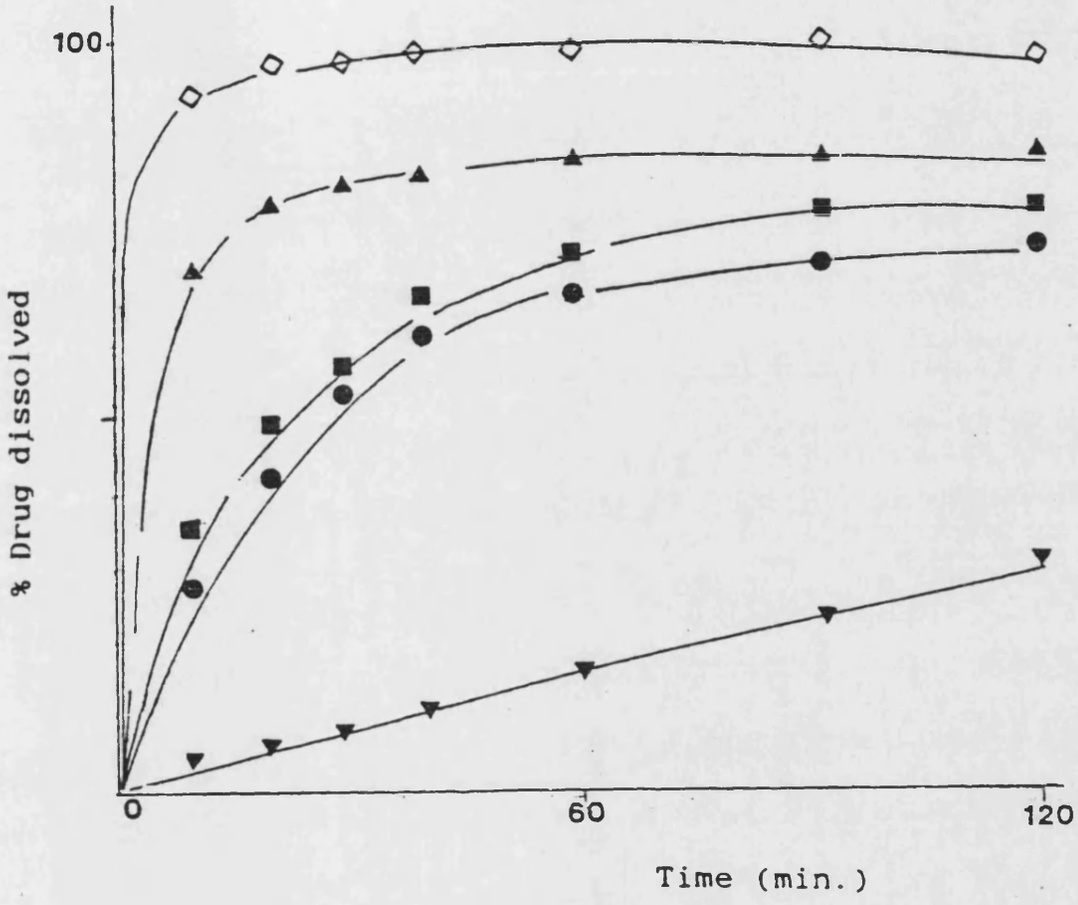


Fig 3.12 The influence of diluent type on the dissolution of drug from capsules containing 100mg phenytoin sodium and 130mg diluent. ◇ drug alone; ● lactose; ■ calcium sulphate; ▲ dibasic calcium phosphate; ▼ calcium chloride



chloride and dibasic calcium phosphate dihydrate. Dissolution characteristics calculated from Kitazawa plots are shown in Table 3.2.

Table 3.2 Dissolution characteristics of phenytoin and phenytoin sodium capsules containing 56% $^{w}/_{w}$ of different diluents

(Values in brackets are correlation coefficients)

Drug	Diluent	k_i (min^{-1})	k_f (min^{-1})	t_1 (min)
phenytoin	-	0.018 (0.997)	0.006 (0.986)	28
	lactose D_3	0.046 (0.999)	0.018 (0.999)	43
	dibasic calcium phosphate dihydrate	0.018 (0.999)	0.006 (0.996)	27
	calcium sulphate dihydrate	0.020 (0.993)	0.005 (0.983)	27
	calcium chloride	0.035 (0.995)	-	-
phenytoin sodium	-	0.450 (1.00)	0.058 (0.996)	4
	lactose D_3	0.038 (0.992)	0.008 (0.982)	25
	dibasic calcium phosphate dihydrate	0.252 (0.998)	0.005 (0.920)	7
	calcium sulphate dihydrate D_5	0.053 (0.999)	0.015 (0.992)	15
	calcium chloride	0.007 (0.988)	-	-

For capsules containing phenytoin alone, the dissolution rate of the drug was very slow with only 36% $^{w}/_{w}$ being dissolved in 30 minutes (Fig. 3.11). When lactose or calcium chloride was added as diluent, a marked improvement in dissolution rate (k_i) was observed (Table 3.2). Only a slight improvement in dissolution rate was observed when calcium sulphate was used as diluent, and no improvement was noted on the addition of

dibasic calcium phosphate (Table 3.2). The dissolution rate of phenytoin sodium from capsules containing only the sodium salt with no additive was higher than for any of the formulations of phenytoin sodium discussed above. All the diluents studied caused a reduction in the dissolution rate of the drug from capsules (Table 3.2).

The effect of type of diluent incorporated was most pronounced in all cases during the initial phase of the dissolution process during which disintegration occurred. The processes involved in the disintegration phase are:

1. the wetting of powder particles
2. penetration of liquid through pores in the powder bed
3. disintegration of the powder bed
4. dissolution of particles.

The wetting involved during dissolution is immersional wetting and involves the replacement of the solid/air interface with the solid-liquid interface (Parfitt, 1981). The energy change involved, E_i, is given by the equation:

$$E_i = -\gamma_{LV}\cos\theta \qquad \text{Equation 3.2}$$

where γ_{LV}, is the surface tension of the liquid at the liquid-vapour interface and θ, the contact angle between the liquid and powder. For wetting to occur spontaneously, E_i must be negative or the contact angle must be less than 90°. Phenytoin is hydrophobic with contact angle of 102° (Lerk, Legas, Lie-A-Huen, Broersma and Zuurman, 1979). Thus unlike phenytoin sodium which is hydrophilic, phenytoin particles will not readily wet and work must be expended on the system for wetting to occur. The rate of penetration of fluid through a porous bed depends amongst other factors on the contact angle. This is given

by a modified version of the Washburn equation:

$$\frac{dl}{dt} = \frac{K \gamma_{LV} \cos \theta}{4 \eta l} \qquad \text{Equation 3.3}$$

where l, is the distance penetrated in time, t; η , the viscosity of the penetrating liquid and K, a factor which contains an effective radius for the bed and a tortuosity factor to account for the irregular path between particles and aggregates. Thus due to the hydrophobic nature of phenytoin, the rate of penetration of fluid in the powder bed will be limited. Another factor which will retard further the dissolution of phenytoin in the disintegration phase, is the extremely low aqueous solubility of phenytoin particles (Table 3.3). This effect is quantified by Equation 1.6 (page 14) which predicts the relationship between the dissolution rate and solubility of drug particles.

For binary mixes containing drug and diluent, it can be assumed that the wettability of the binary blend is an additive function of the proportions and wettability of the individual components. Contact angles for lactose and dibasic calcium phosphate have been found by Lerk, Schoonen and Fell (1976) to be 30° and 0° respectively. One would expect that if the dissolution rate of binary formulations was determined by wettability alone, dissolution from capsule formulations containing phenytoin/dibasic calcium phosphate would be faster than from those containing lactose as diluent. In the case of phenytoin (Fig. 3.11) this was not so. However, a consideration of the solubility of the diluents (Table 3.3) indicates that the solubility of the diluent incorporated determined the dissolution rate from capsules of phenytoin. The higher the solubility of the diluent, the faster the dissolution rate observed.

Table 3.3 Solubilities of drug and diluent powders in water at 25°C

Powder	Solubility (g l^{-1})
phenytoin	0.1
phenytoin sodium	15.2 (Merck Index, 1984)
lactose	213.8
calcium sulphate dihydrate	2.6
dibasic calcium phosphate	0.1 (Mullin, 1972)
calcium chloride	882.5 (Mullin, 1972)

From the above date (Table 3.3), it appears that the presence of hydrophilic soluble diluents improves the dissolution of a hydrophobic drug, such as phenytoin. When penetrating liquid dissolves soluble diluent particles in a powder bed the penetration of fluid through the bed is improved. As a result, the hydrophobic phenytoin particles are wetted more effectively and maximum surface area of the drug is exposed to the dissolution medium resulting in improved dissolution. These findings are consistent with the work of Newton and Razzo (1977) who found that wetting alone was not the controlling factor in the release characteristics of a hydrophobic drug but rather the solubility of the diluent.

For capsule formulations containing phenytoin sodium the extent of retardation (Table 3.2) appeared to be associated with the solubility of the diluent. The higher the solubility of the diluent, the greater the retardation observed. The effect appears to be most significant during the disintegration phase since k_i values varied greatly depending on the type of diluent. This would suggest that the effect on dissolution

was associated with changes occurring in the powder bed during this stage. The topic is discussed in Section 3.2.2.2.

3.2.2.2 The effect of diluent concentration

The results in Fig. 3.13 show the influence of adding increasing concentrations of either lactose or calcium sulphate dihydrate on the dissolution of phenytoin sodium from a capsule. The dissolution parameter, percentage dissolved in 30 minutes, W_{30}, has been used to provide a single value by which dissolution from the capsule formulations could be compared. This is because, despite the fact that the percentage of drug versus time was non-linear in all cases, in most of the formulations the rate of dissolution was normally determined within the first 30 minutes. Initially, an increase in the proportion of diluent led to a retardation in dissolution rate to a minimum value during a phase defined as Phase I. When the diluent concentration was increased above a certain critical value, the release rate increased - Phase 2. Only in formulations where 95% lactose was incorporated as diluent was the dissolution rate higher than for capsules containing drug alone. The dissolution parameters calculated from the corresponding Kitazawa plots are summarised in Table 3.4. With increasing diluent concentration, the dissolution rate constants k_i and k_f were both reduced at first. Beyond the minimum value, at a diluent concentration of approximately 70% $^{w}/_{w}$, the dissolution rate constants k_i and k_f were increased. Capsules containing 95% lactose showed only a single rectilinear dissolution profile when the Kitazawa plot was drawn. This indicates the rate was constant throughout the the dissolution suggesting that there was a continuous generation of surface area of the drug into the dissolution medium.

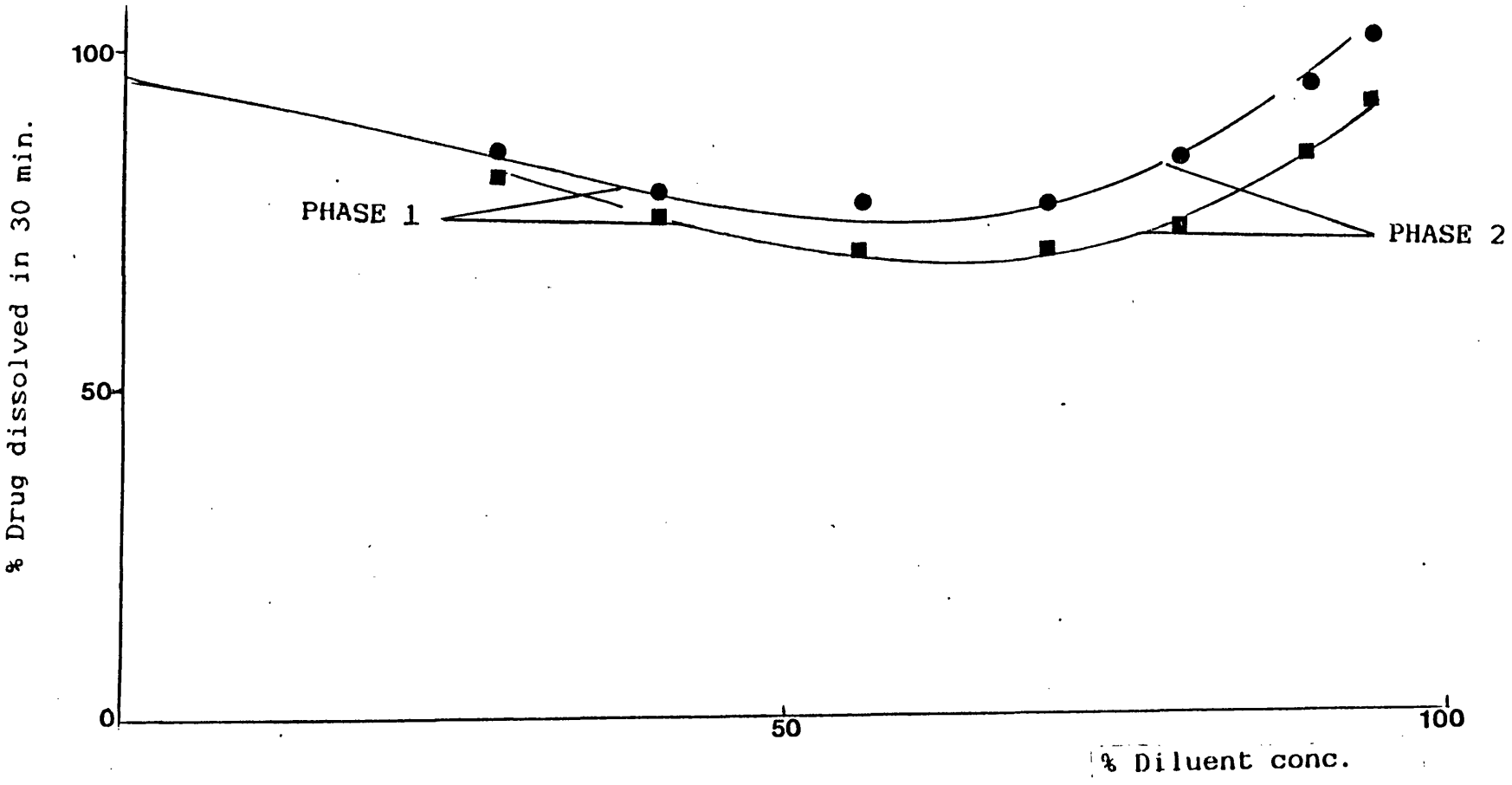


Fig. 3.13 The influence of diluent concentration on percentage of phenytoin sodium dissolved in 30 minutes

● lactose D_1; ■ calcium sulphate dihydrate D_4

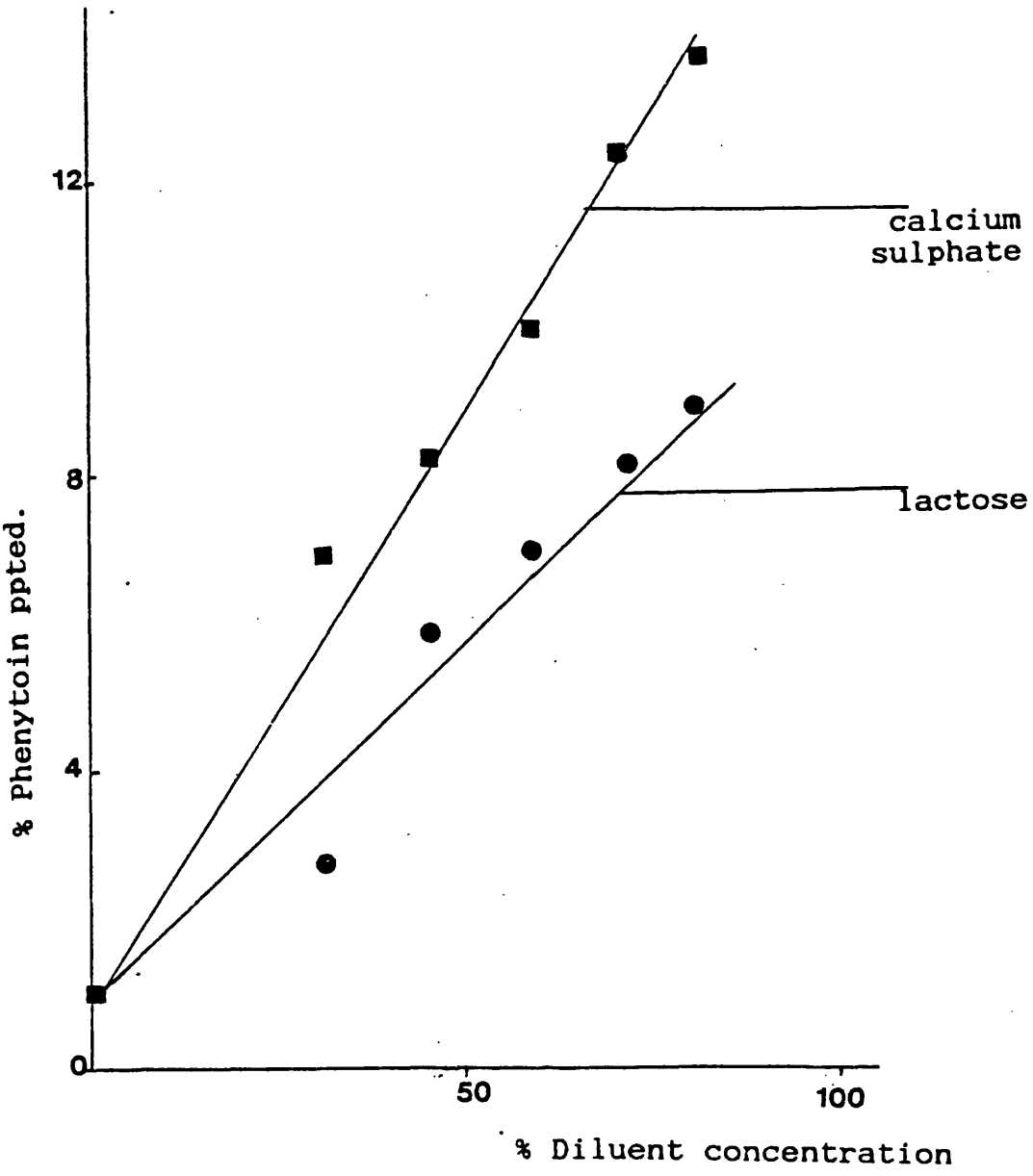
Table 3.4 Dissolution characteristics of phenytoin sodium capsules showing the effect of adding increasing concentrations of either lactose D_1 or calcium sulphate D_4

Diluent	Diluent conc. % $^{w}/_{w}$	k_i (min^{-1})	k_f (min^{-1})	t_1 (min)
Lactose D_1	0	0.450 (1.00)	0.058 (0.996)	4
	29	0.140 (0.991)	0.009 (0.970)	10
	56.5	0.049 (0.999)	0.010 (0.986	17
	70	0.035 (0.999)	0.020 (0.988)	28
	80	0.059 (0.998)	0.026 (0.998)	16
	90	0.105 (0.992)	0.070 (0.992)	10
	95	0.148 (0.997)	-	-
Calcium sulphate dihydrate D_4	0	0.450 (1.00)	0.058 (0.996)	4
	29	0.043 (0.999)	0.023 (0.995)	8
	56.5	0.017 (0.998)	0.009 (0.990)	18
	70	0.031 (0.996)	0.009 (0.996)	26
	80	0.050 (0.991)	0.011 (0.995)	20
	90	0.072 (0.999)	0.013 (0.989)	16
	95	0.073 (0.999)	0.014 (0.984)	15

It was noted that capsules containing 50-70% diluent did not disintegrate readily, also a slowly dissolving precipitate was seen to form at the bottom of the dissolution vessel. By analysing this deposit which formed within 5 minutes, it was found that the insoluble acid form phenytoin had been precipitated, although the pH of the dissolution medium was 9. The precipitate was observed even in capsules of drug alone. An increase in the proportion of diluent increased the amount of phenytoin which was precipitated, the largest quantities were detected when calcium sulphate was used as diluent (Fig. 3.14). The effect probably explains the retardation effect of diluents on the release of drug in Phase I. When insoluble phenytoin is precipitated at the bottom of the vessel, the dissolution rate constants will be reduced.

Capsules containing 300mg calcium sulphate alone take longer than two hours to dissolve whilst those of lactose are fully dissolved in 20-30 minutes because of its higher solubility. Any phenytoin which is precipitated during the course of dissolution will initially have been in contact with one or the other of these diluents. The dissolution of phenytoin in its acid form has been shown to be more rapid in the presence of soluble diluents (see Fig. 3.11). Thus capsules formulated with phenytoin and lactose show faster dissolution than those formulated with calcium sulphate. Following this argument, it is possible that in formulations containing lactose, a higher proportion of phenytoin is precipitated and then quickly redissolved. As a result when phenytoin levels are sampled, when the dissolution is stopped at 5 minutes, lower levels of phenytoin may be detected than is actually precipitated. Fig. 3.15a shows a photomicrograph of undissolved calcium sulphate particles covered with needle and plate-like particles. Fig. 3.15b shows a photomicrograph at higher

Fig. 3.14 The influence of diluent concentration and type on the percentage phenytoin precipitated during the dissolution of phenytoin sodium capsules



magnification and Fig. 3.15c, the corresponding X-ray dot mapping for Ca^{2+}. This shows that calcium phenytoin has been crystallized on the surface of the calcium sulphate particles. The diffusion layer around the calcium sulphate particles contains various ions including phenytoin and calcium, and the calcium salt of the drug is precipitated when its solubility is exceeded within the diffusion layer. Phenytoin is also probably adsorbed from solution on to the calcium sulphate surface.

The exact mechanism by which these diluents facilitate the precipitation of phenytoin is unclear. However, it is known that for crystallization or precipitation to occur a super-saturated solution must be formed. Also nuclei or seed crystals should be present to initiate crystal growth (Yalkowsky and Valvani, 1977). When capsule formulations of phenytoin sodium are penetrated by fluid, the drug particles are immediately hydrated with an associated release of heat. Also, the volume of dissolution fluid which initially penetrates the powder bed in capsule shell is small; so the buffer capacity of the borate buffer used as dissolution medium will be exceeded. The pH of the microenvironment around the dissolving drug particles, that is the diffusion layer pH, will be equivalent to the pH of a saturated solution of phenytoin sodium that is greater than 11.7. Thus because of the exothermic reaction and the extremely high pH of the diffusion layer, the solubility of phenytoin will be exceeded and a super-saturated solution will exist.

Nucleation may occur heterogenously due to the presence of foreign bodies such as intact diluent particles. However, the fact that the phenytoin precipitation appears to be related to diluent solubility would indicate that the effect was associated with dissolving diluent particles. Concentrated solutions of lactose and calcium sulphate in

Fig 3.15a) Photomicrograph of undissolved calcium sulphate particle after 30 min. of dissolution.
b) photomicrograph of same surface at higher magnification.
c) X-ray dot mapping for Calcium ion.

a)

x 200

100 μm

b)

x 4300

10 μm

c)

x 4300

10 μm

borate buffer (pH 9.0) have a pH of 7.20 and 8.86 respectively. Probably, when the super-saturated phenytoin solution comes in contact with the diffusion layers around diluent particles, phenytoin will be precipitated due to the drop in pH.

From Table 3.5 consolidated powder beds of phenytoin sodium could not be penetrated by saturated solutions of calcium chloride due to the precipitation of insoluble phenytoin around the phenytoin sodium particles. This observation would explain the extremely low rate of dissolution of phenytoin sodium in the presence of calcium chloride (Table 3.2). When diluent particles are almost insoluble, as in the case of dibasic calcium phosphate, the dissolution rate is similar to that of drug alone. Therefore in the development of capsule formulations containing phenytoin sodium it is worth noting that the presence of any soluble excipient whose diffusion layer pH will facilitate the precipitation of phenytoin, is likely to lead to the lowering of dissolution rate as compared to that of drug alone. Presumably only the incorporation of strong disintegrants which will facilitate the dispersion of phenytoin sodium particles will lead to improvement of the dissolution rate.

Table 3.5 The influence of different penetrating liquids on the swelling capacity of a packed powder bed of phenytoin sodium of porosity 0.62

Penetrating liquid	Swelling capacity, S_c
water	0.6
borate buffer (pH 9.0)	0.5
sodium hydroxide solution (0.01M)	0.5
calcium sulphate (saturated solution)	0.4
lactose (saturated solution)	0.5
calcium chloride (saturated solution)	no penetration *

*precipitation of phenytoin occurred

3.2.2.3 Effect of diluent particle size

The results showing the influence of particle size and concentration of diluent on dissolution of phenytoin sodium from capsule formulations are shown in Fig. 3.16a, b and c. The graphs indicate that, for capsules containing lactose D_1 (Fig. 3.16a) or lactose D_2 (Fig. 3.16b) or calcium sulphate D_4 (Fig. 3.16c), diluent particle size had a significant effect on dissolution rate, when the diluent concentrations exceeded 30% $^{w}/_{w}$. Dissolution was faster from capsules containing the larger size diluents than for the smaller size. The effect of diluent particle size was less pronounced in lactose D_2 formulations (Fig. 3.16b).

These results may be explained by considering the likely pore structure within the powder bed. Although fine diluent particles probably provide a structure of higher porosity, the dimensions of pore spaces or the capillary radii will be very much smaller than when coarse particles are used, liquid penetration through the powder bed will be reduced with a resulting decrease in dissolution rate. Thus it is not the packing fraction alone which must be taken into consideration but also the pore dimensions. These results are in agreement with the findings of other workers (Newton and Rowley, 1970; Newton and Bader, 1980). Another plausible explanation may be the improved mutual distribution of diluent and drug particles when the diluent particle size is reduced. Since the presence of soluble diluents have been shown (Section 3.2.2.1) to cause drug-diluent interactions during dissolution, larger areas of interfacial contact may lead to greater interaction with a consequent increase in the amount of phenytoin precipitated.

Fig. 3.16a

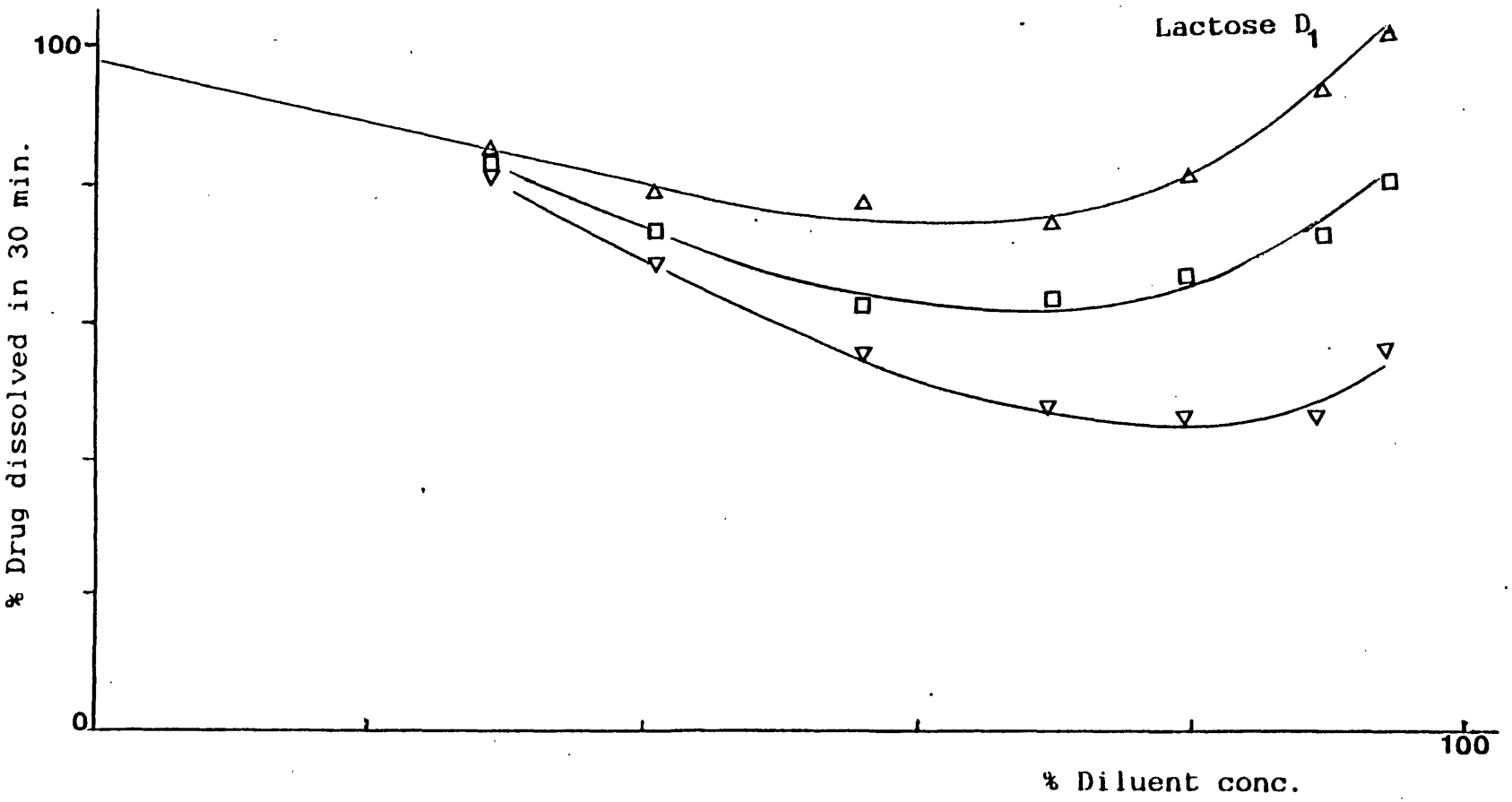


Fig. 3.16 The influence of the diluent particle size and concentration on the percentage of phenytoin sodium dissolved in 30 minutes Particle size of drug was $<45\mu m$; Diluent particle size:

△ 250-355μm
□ 90-125μm
▽ < 45μm

Fig. 3.16b

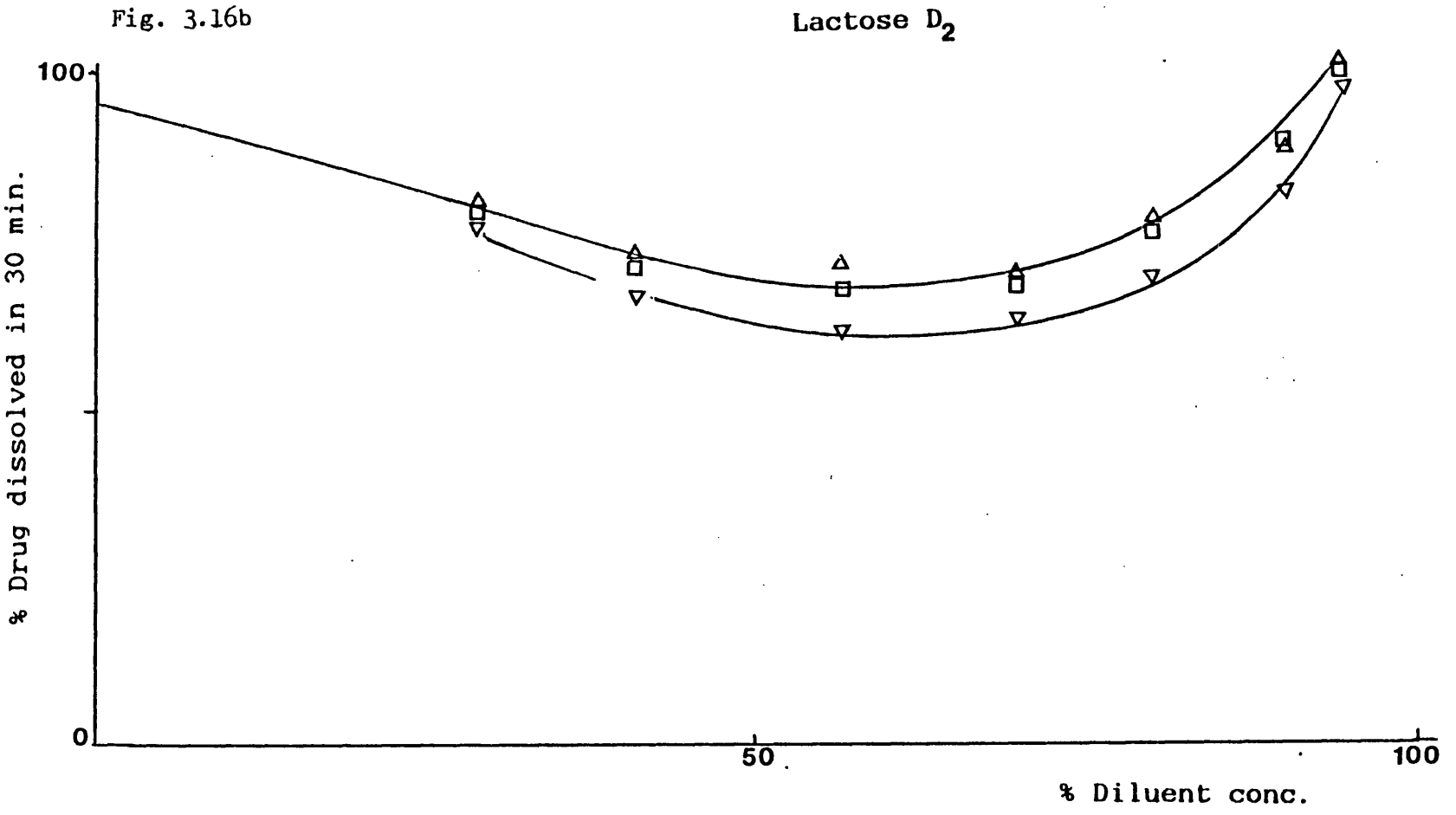
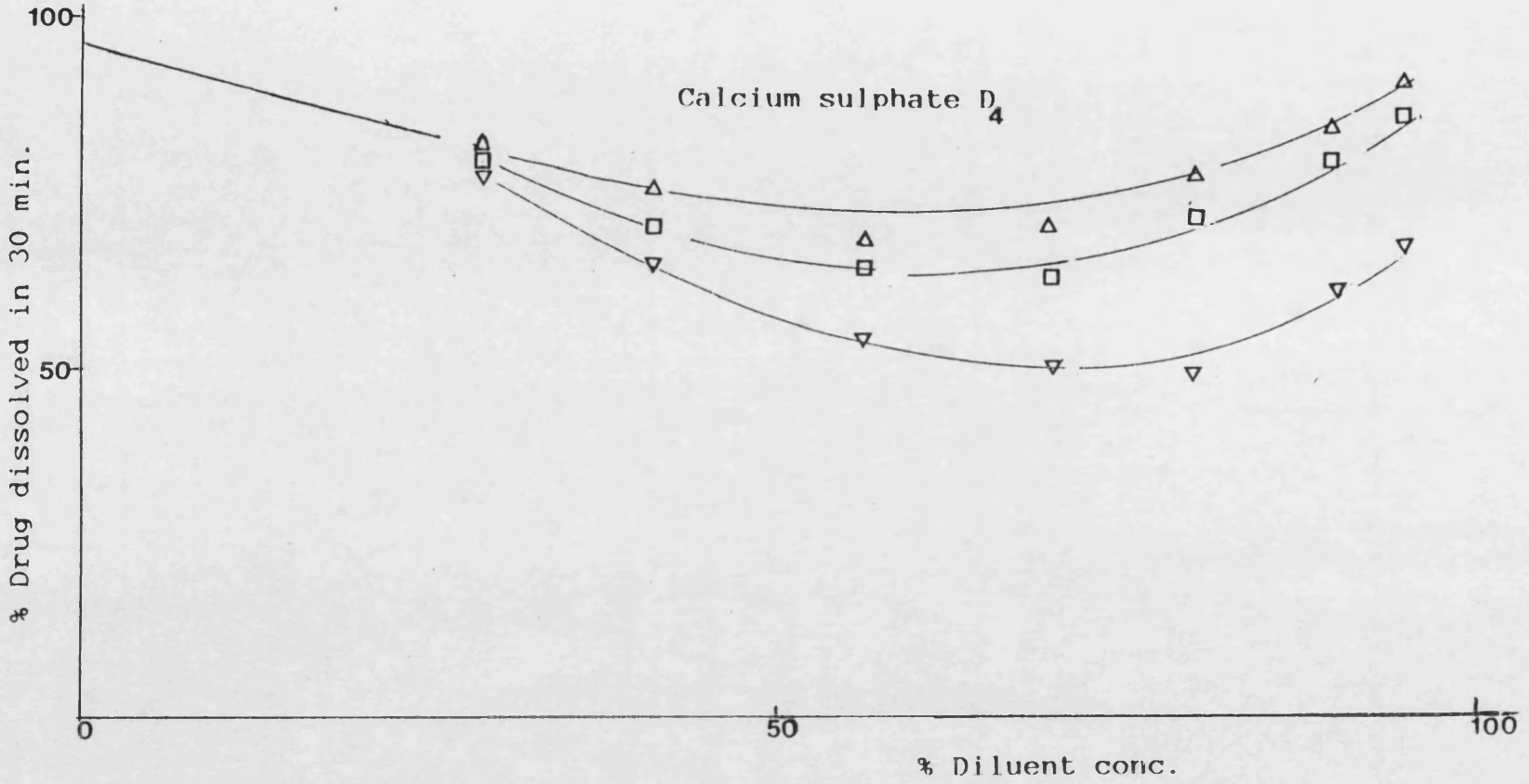


Fig. 3.16c


Calcium sulphate D4
100
50
0
50
100
% Drug dissolved in 30 min.
% Diluent conc.

3.2.3 Three-component formulations

3.2.3.1 Effect of lubricant concentrations

The results showing the effect of adding increasing quantities of magnesium stearate batch L_1 to a binary mix containing 100mg phenytoin sodium and 130mg diluent; lactose D_3 or calcium sulphate D_5 are shown in Fig. 3.17 and Fig. 3.18 respectively. The Kitazawa dissolution rate constants and calculated disintegration times are shown in Table 3.6. Table 3.6 indicates that the effect of lubricant was most pronounced during the k_i phase. There was an improvement in the dissolution rate constant on the addition of up to 0.5% magnesium stearate. At the 5% lubricant level, dissolution from capsules containing lactose was retarded whilst there was no significant effect on dissolution in formulations containing calcium sulphate. Where dissolution rates were increased, disintegration times t_1 were also reduced.

Table 3.6 The influence of magnesium stearate concentration on dissolution characteristics of capsules containing 100mg phenytoin sodium and 130mg diluent (values in brackets refer to correlation coefficient)

Diluent	Lubricant conc. %	k_i (min^{-1})	k_f (min^{-1})	t_1 (min)
Lactose D_3	0	0.038 (0.992)	0.008 (0.981)	25
	0.05	0.048 (0.999)	0.007 (0.995)	21
	0.5	0.059 (0.997)	0.013 (0.999)	18
	5.0	0.028 (0.992)	0.005 (0.940)	32
calcium sulphate dihydrate D_5	0	0.053 (0.999)	0.015 (0.992)	24
	0.05	0.059 (0.997)	0.013 (0.992)	20
	0.5	0.057 (0.997)	0.013 (0.990)	19
	5.0	0.054 (0.999)	0.011 (0.999)	21

Fig. 3.17 The influence of increasing concentrations of Mg stearate on the dissolution of drug from capsules containing 100mg Phenytoin Na and 130mg lactose D_3

Magnesium stearate concentration ◇ 0, ■ 0.05, ● 0.5, ▲ 5.0% $^{w}/_{w}$

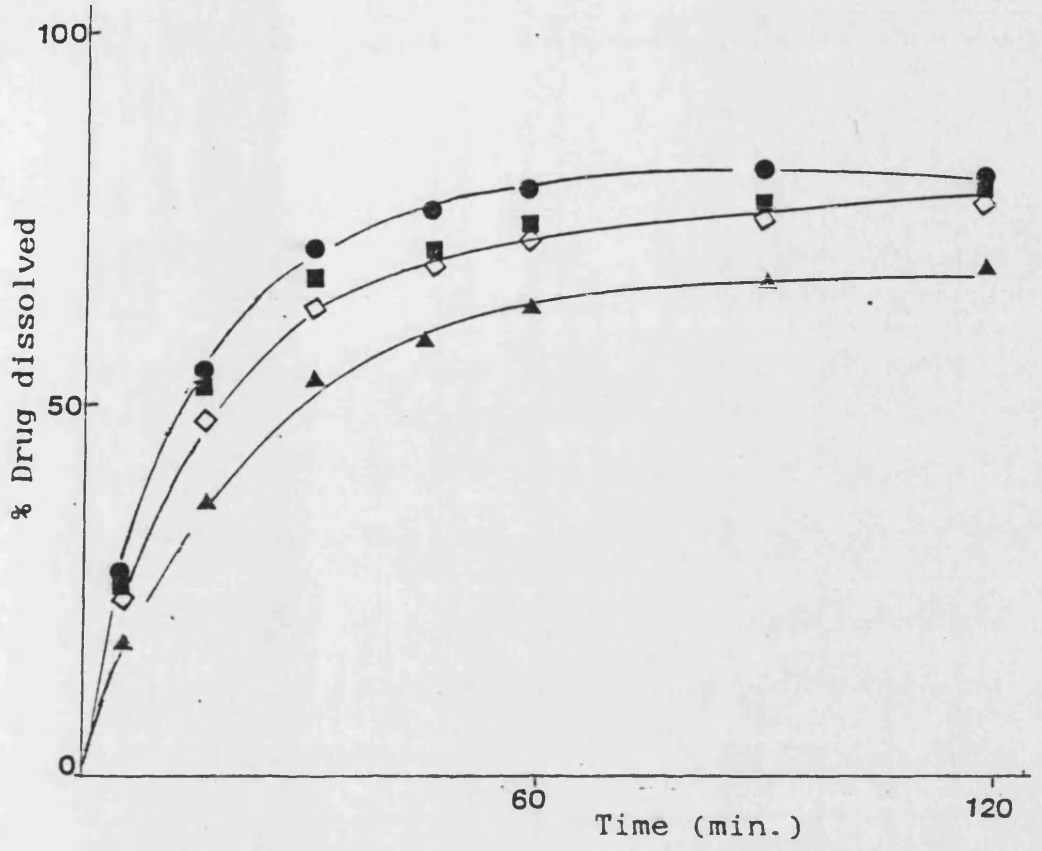
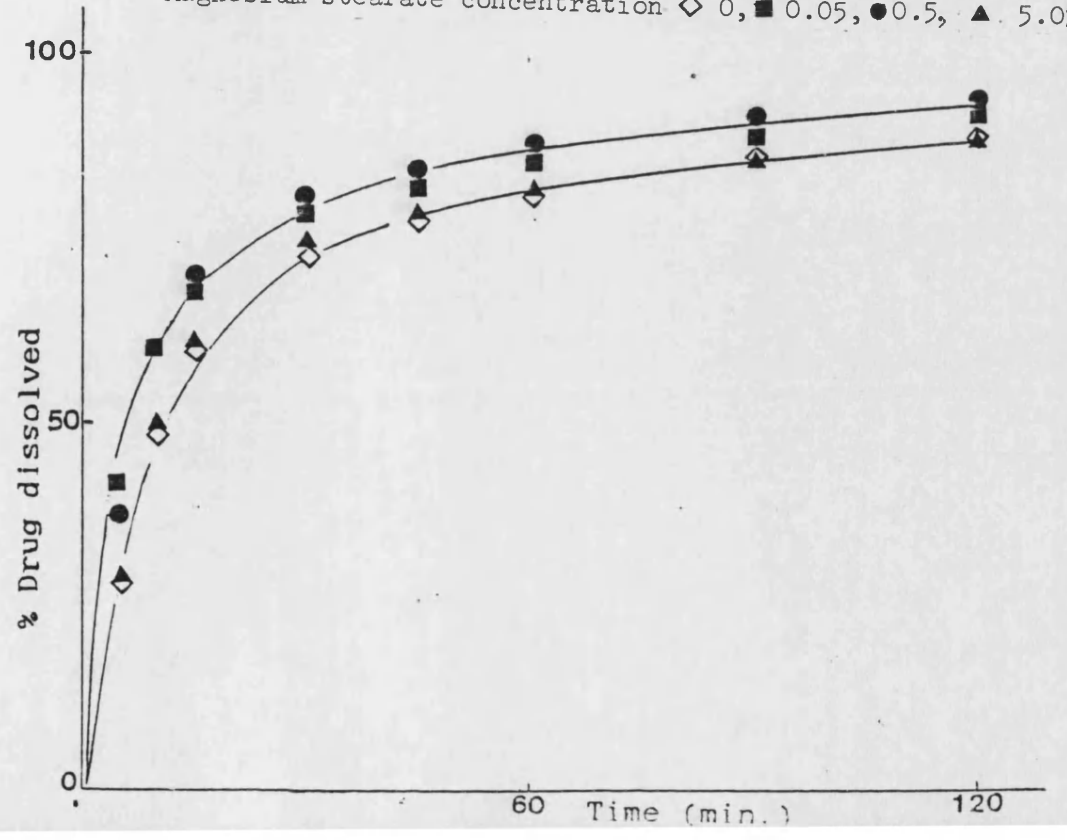


Fig. 3.18 The influence of increasing concentrations of Mg stearate on the dissolution of drug from capsules containing 100mg Phenytoin Na and 130mg calcium sulphate D_5.

Magnesium stearate concentration ◇ 0, ■ 0.05, ● 0.5, ▲ 5.0% $^{w}/_{w}$



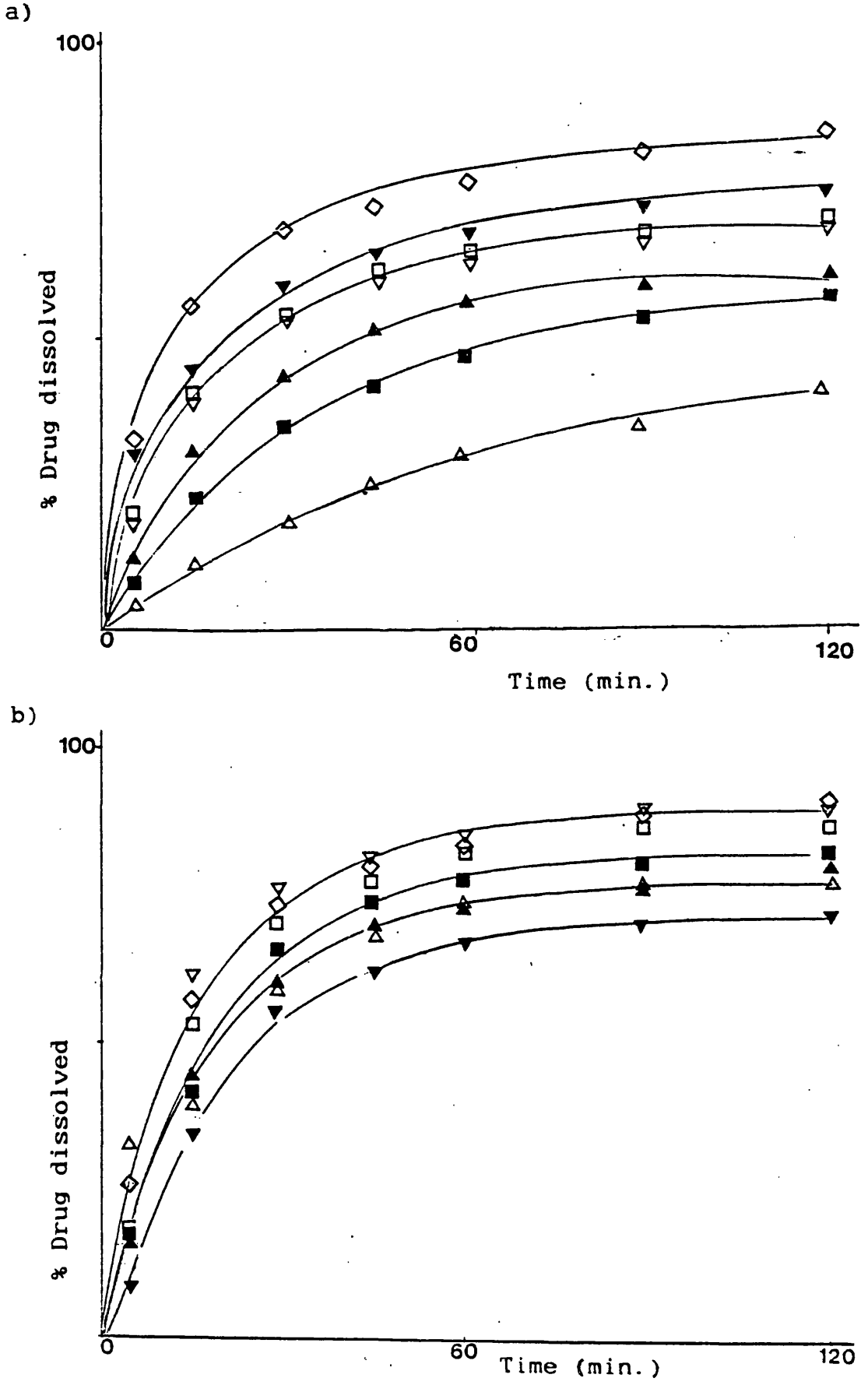
Magnesium stearate is hydrophobic and a contact angle of 121° has been reported for powder compacts (Lerk, Schoonen and Fell, 1976). It is also insoluble in aqueous media (Merck Index, 1984). Therefore it will be expected that addition of magnesium stearate will decrease the wettability of a powder mix, or increase the hydrophobicity with a resulting decrease in dissolution rate. The observed improvement in dissolution rates indicates that other factors are involved. Similar improvement in dissolution rates have been cited in the literature (Newton and Razzo, 1974) with no satisfactory explanation so far. Two possible effects may explain this observation. Since the presence of diluent has been shown to retard dissolution of phenytoin sodium (Section 3.2.2.2), the observed improvement in dissolution rate suggests that the magnesium stearate inhibited the effect of the diluent. It is feasible that the lubricant particles either interact preferentially with diluent forming a hydrophobic film around diluent particles or they may modify the spatial distribution of drug and diluent particles such that drug particles are free within the mix and are easily dispersed during dissolution. These effects are considered in Section 3.5.

3.2.3.2 Effect of batch-to-batch variation in magnesium stearate

The results showing the influence of 5% $^{w}/_{w}$ of the different batches of magnesium stearate on dissolution from capsules containing 100mg phenytoin sodium and 130mg diluent, lactose D_3 or calcium sulphate D_5 are shown in Fig. 3.19 a and b respectively. Capsule formulations containing lactose showed a wide variation in dissolution rate, W_{30} values ranged from 20.0 to 60.3%. Formulations containing calcium sulphate showed less variation with W_{30} values ranging from 55.3 to

Fig. 3.19 The influence of the various batches of magnesium stearate (5% $^{w}/_{w}$) on the dissolution profile of capsules containing 100mg phenytoin sodium and 130mg diluent. (a) lactose D_3 (b) calcium sulphate D_5

◇ no lubricant; ▽ L_1; ▼ L_2; △ L_3; ■ L_4; □ L_5; ▲ L_6.



74.0%. The dissolution rate constants calculated from the dissolution profiles are shown in Table 3.7.

Table 3.7 Dissolution characteristics of phenytoin sodium capsules showing the effect of different batches of magnesium stearate.

Diluent	Mg stearate batch	Dissolution rate k_i (min^{-1})	Dissolution rate k_f (min^{-1})	Disintegration time t_1 (min)
Lactose D_3	L_1	0.023 (0.992)	0.005 (0.940)	32
	L_2	0.020 (0.961)	0.004 (0.992)	35
	L_3	0.004 (0.987)	-	-
	L_4	0.009 (0.995)	0.003 (0.999)	75
	L_5	0.023 (0.994)	0.005 (0.971)	34
	L_6	0.015 (0.997)	0.003 (0.975)	45
Calcium sulphate D_5	L_1	0.054 (0.999)	0.011 (0.999)	21
	L_2	0.024 (0.999)	0.004 (0.991)	37
	L_3	0.031 (0.999)	0.005 (0.999)	34
	L_4	0.034 (0.999)	0.007 (0.995)	34
	L_5	0.052 (0.999)	0.008 (0.971)	23
	L_6	0.039 (0.999)	0.006 (0.999)	22

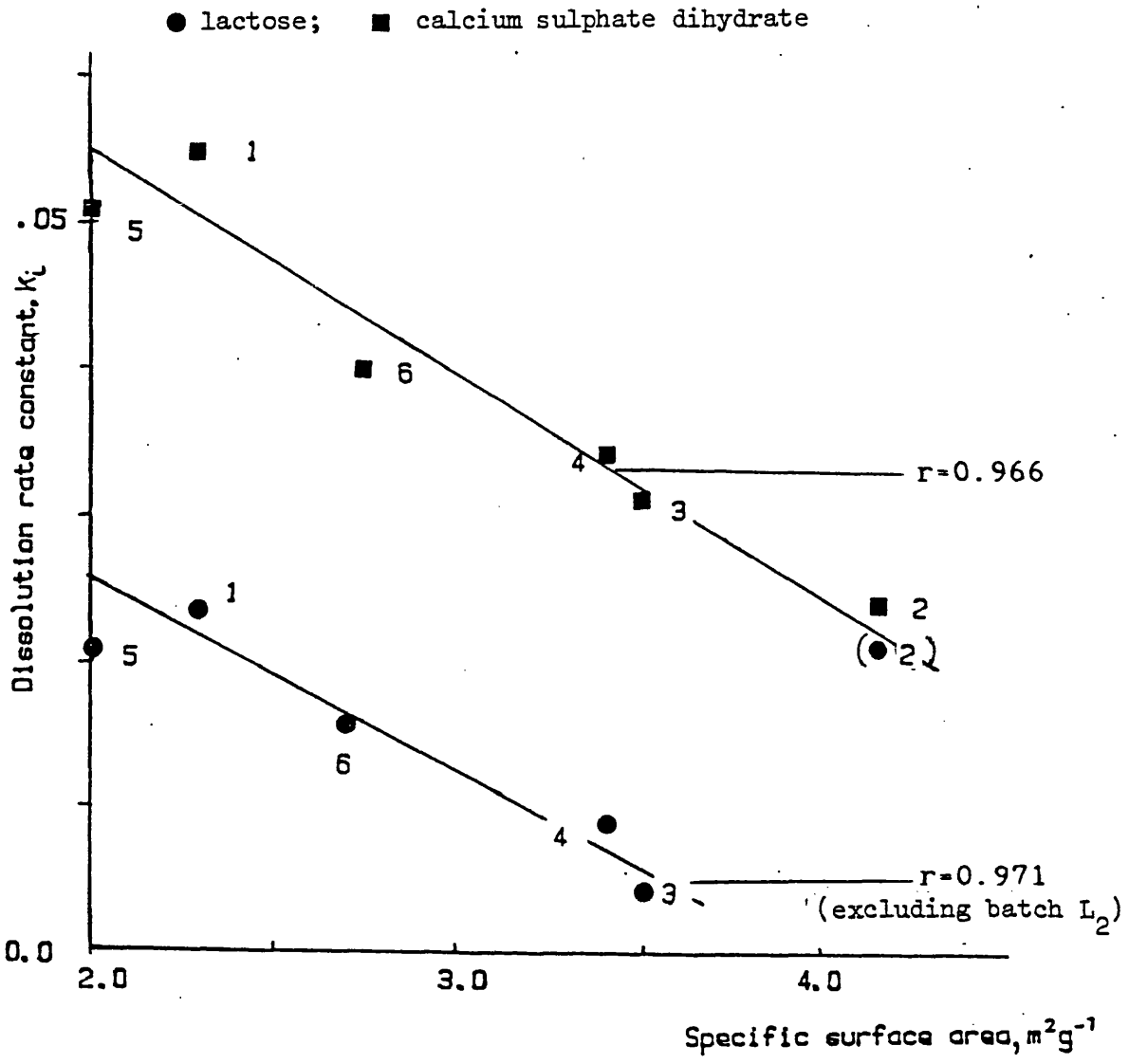
From Table 3.7, the effects of batch-to-batch change in the lubricant on dissolution were most pronounced during the k_i phase. These differences were obviously due to variation in properties of the batches of magnesium stearate

There were significant differences in particle sizes and particle shape (Fig. 2.1) of the magnesium stearate powders. Particles were basically plate-like in all the six batches except for batch L_2, which

contained a few agglomerates of needle-like particles. It is known that plate-like crystals are produced under acidic conditions during the manufacture of magnesium stearate and needle-like crystals under alkaline conditions (Miller, York and Jones, 1982). This would suggest that there was inadequate control of pH during the manufacture of batch L_2. The specific surface diameters of lubricant powders varied from 1.40μm for batch L_2 to 2.70μm for batch L_5 (Table 2.3). Due to the high surface force as compared to gravitational forces these particles form agglomerates of average diameters ranging from 10 to 12μm. The differences in particle diameters were also obvious during the study of the consolidation behaviour of the lubricants (Fig. 2.2), with batch L_2 showing the least change in packing density with packing. The measurement of electrostatic charge developed on the lubricant surface after contact with metal surface also showed a wide variation (Table 2.7). All the different batches showed electropositive charge with batch L_3, L_4, and L_5 showing the highest charges and L_1, L_2 and L_6 the least. However, despite these differences, the effect of batch-to-batch change on dissolution rate could simply be correlated to the specific surface area of the lubricant for formulations containing calcium sulphate or lactose (excluding batch L_2) (Fig. 3.20). With an increase in specific area of lubricant, the drug dissolution rate was reduced. These correlations are obtained during the k_i phase, therefore the effect most likely is related to the ability of dissolution fluid to penetrate the pore structure of the powder bed.

Billany and Richards (1981) have found that the batch-to-batch variation of magnesium stearate could be attributed to differences in surface-active water-soluble impurities which are leached out during the dissolution process. These impurities are presumed to reduce

Fig. 3.20 Correlation of specific surface area of magnesium stearate with dissolution rate k_1.



surface tension at the solid/liquid interface with a resultant decrease in contact angle, improved wettability and better solid-liquid contact. The relationship between surface tension and contact angle is given by the Young-Dupre's equation:

$$\gamma_{LV} \cdot \cos\theta = \gamma_{SV} - \gamma_{SL} \qquad \text{Equation 3.4}$$

where γ, is the interfacial tension and the subscripts S, L and V refer to the solid, liquid and vapour phases respectively. However, in the present study, the observed retardation could not be correlated with the surface tension of the water soluble impurities (Table 2.3). Interestingly capsule formulations containing lactose and magnesium stearate L_2 showed faster release rate than would be expected based on its particle size. The surface tension of the water soluble impurities was also the least - $59 mNm^{-1}$ (Table 2.3) - suggesting that these impurities modified the dissolution behaviour. With the experiments of Billany and Richards (1981), the lubricant level in tablets was 1% $^{w}/_{w}$ and the poorly soluble drug, acetyl salicylic acid, was used. Presumably for such a formulation, the tablet remains intact during the dissolution process, and the rate of dissolution is no longer determined by the size of permeable pores within the compact. Rather the levels of the surface-active impurities or the wettability of the compact determine the rate of dissolution. It is therefore possible that for drugs of very poor solubility, lubricant levels in the range normally used in industry (0.5 - 2% $^{w}/_{w}$) may allow the dosage form to remain as a compact and for such formulations these surface-active impurities may modify the dissolution rate.

3.2.3.3 Effect of mixing sequence

The initial experiments on the effect of mixing sequence were performed using capsules containing 100mg phenytoin sodium and 130mg diluent (i.e. 56.5% $^{w}/_{w}$ diluent). Magnesium stearate concentrations used were 0, 0.05, 0.5 and 5.0% $^{w}/_{w}$. The dissolution profiles obtained are shown in Fig. 3.21a for selected formulations containing lactose D_3 as the diluent and in Fig. 3.21b for calcium sulphate D_5. Dissolution parameters calculated from the dissolution data are shown in Table 3.8 and Table 3.9. The mixing sequences (P-D, P-D-L, D-L-P, P-L-D) have been defined in Section 2.2.3.4.

Table 3.8 The influence of magnesium stearate concentration and mixing sequence on the dissolution characteristics of phenytoin sodium capsules containing 56.5% lactose D_3 as diluent

Magnesium stearate conc. % $^{w}/_{w}$	Mixing Sequence	k_i (min^{-1})	k_f (min^{-1})	t_1 (min)
0	P-D	0.038 (0.992)	0.008 (0.981)	25
0.05	P-D-L	0.048 (0.999)	0.007 (0.995)	21
	D-L-P	0.048 (0.989)	0.007 (0.999)	20
	P-L-D	0.042 (0.999)	0.008 (0.995)	22
0.5	P-D-L	0.059 (0.997)	0.013 (0.999)	18
	D-L-P	0.058 (0.989)	0.010 (0.992)	20
	P-L-D	0.036 (0.974)	0.008 (0.989)	20
5.0	P-D-L	0.028 (0.992)	0.005 (0.940)	32
	D-L-P	0.032 (0.994)	0.005 (0.939)	26
	P-L-D	0.019 (0.989)	0.006 (0.986)	30

Fig. 3.21 The influence of mixing sequence on the dissolution profile of capsules containing 100mg phenytoin sodium and (a) 130mg lactose D_3 and 5% magnesium stearate; (b) 130mg calcium sulphate dihydrate D_5 and 0.5% magnesium stearate

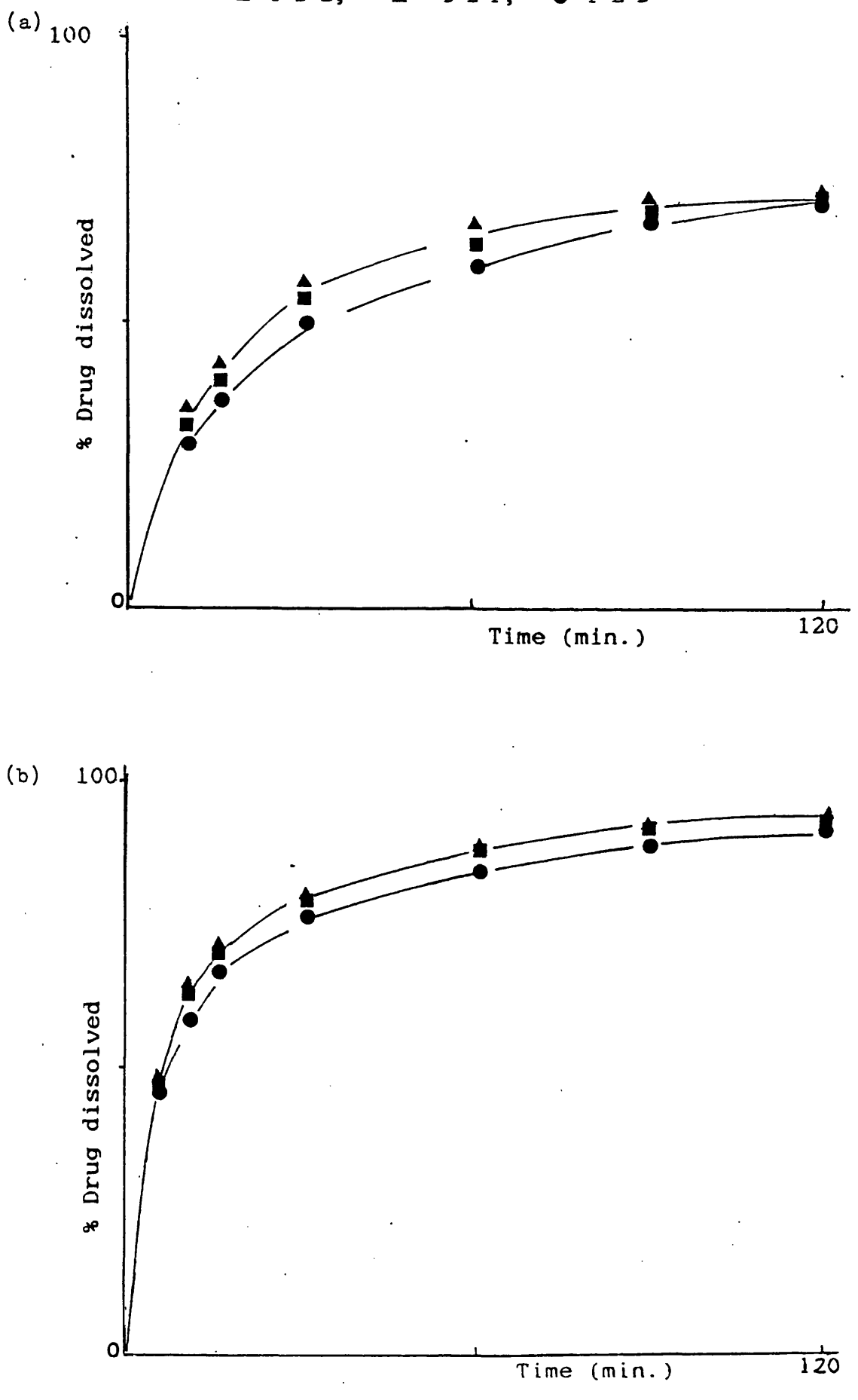


Table 3.9 The influence of magnesium stearate concentration and mixing sequence on the dissolution characteristics of phenytoin sodium capsules containing 56.5% calcium sulphate D_5 as diluent

Magnesium stearate conc. % w/w	Mixing Sequence	k_i (min^{-1})	k_f (min^{-1})	t_1 (min)
0	P-D	0.053 (0.999)	0.015 (0.992)	24
0.05	P-D-L	0.059 (0.997)	0.013 (0.992)	20.
	D-L-P	0.058 (0.998)	0.013 (0.992)	20
	P-L-D	0.054 (o.999)	0.009 (0.965)	24
0.5	P-D-L	0.057 (0.997)	0.013 (0.992)	19
	D-L-P	0.056 (0.994)	0.013 (0.990)	21
	P-L-D	0.050 (0.990)	0.012 (0.994)	19
5.0	P-D-L	0.054 (0.999)	0.011 (0.999)	21
	D-L-P	0.052 (0.999)	0.010 (0.987)	22
	P-L-D	0.045 (0.996)	0.010 (0.994)	23

The influence of mixing sequence was most pronounced during the disintegration stage, k_i, of the dissolution process. The effect of mixing sequence was statistically significant ($p < 0.1$) for 0.5% lubricant in capsules containing calcium sulphate and 5% lubricant in lactose capsules. In each case a higher dissolution rate k_i was observed when diluent particles were first in contact with lubricant in the sequence D-L-P than when drug was first mixed with lubricant, P-L-D. Dissolution rate constants for the mixing sequence P-D-L were comparable to those in D-L-P mixes. These differences were achieved using identical components, with only the mixing sequence during processing being varied. It is thus clear that these differences are due to changes in spatial arrangement of the three components within the mix.

Magnesium stearate particles are known to confer hydrophobicity on substrate particles to which they adhere and therefore it would be expected that in P-L-D mixes a hydrophobic film around drug particles will retard dissolution rate. In D-L-P mixes, lubricant particles may form a film around diluent which may retard the dissolution of diluent and thereby improve the overall dissolution rate as compared to P-L-D mixes. Another possibility is the proportion of lubricant particles interacting with drug particles may be less in D-L-P mixes than in P-L-D mixes. Dissolution rates from P-D-L mixes were similar to those of D-L-P suggesting that the overall spatial structure of particles in the two mixing sequence were similar.

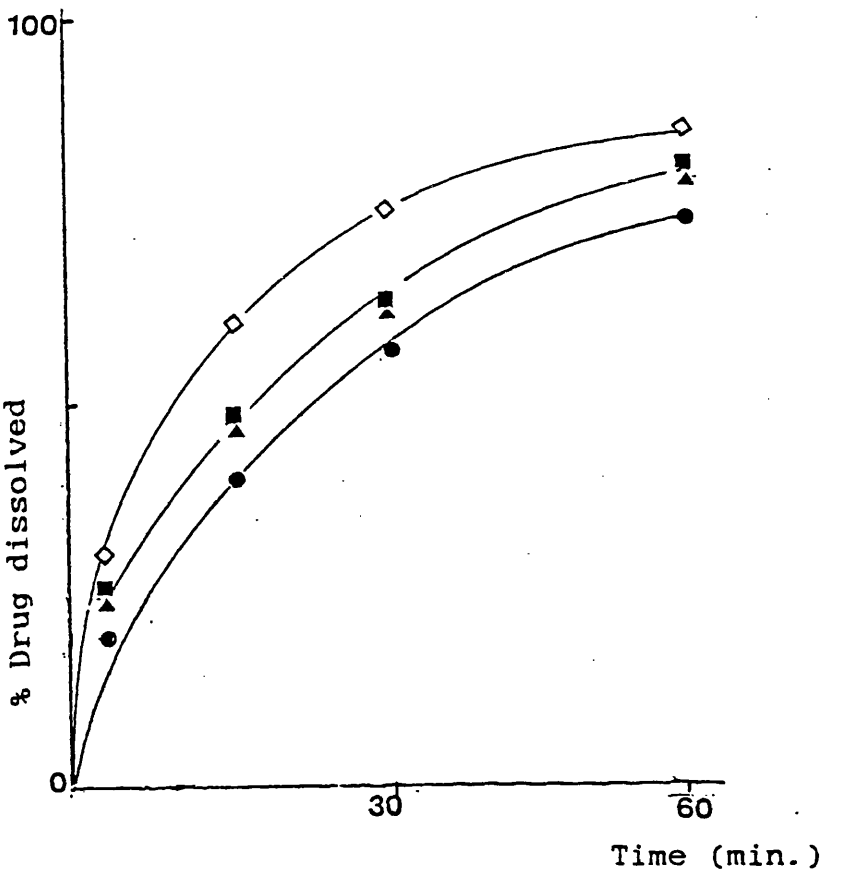
The second part of the study involved a change in particle size of drug and diluent to improve drug-diluent particle interactions in the solid state. In the first part of the study (see above), drug particle size was $<45\mu m$ and the diluent size was 250-355μm. Diluent concentrations were up to 95% and the three diluents lactose D_1, lactose D_2 and calcium sulphate D_4 were used. Significant differences in dissolution profiles were observed only when the diluent concentrations were high corresponding to Phase 2 of the experiments discussed in Section 3.2.2.2. Fig. 3.22, 3.23 and 3.24 show the influence of mixing sequence on dissolution profile for the diluents D_1, D_2 and D_4 respectively, the two graphs in each figure represent diluent concentrations of 80 and 95%. There were also significant differences between the dissolution profiles when the two types of lactose, diluent D_1 and D_2, were used.

Two types of patterns were noted. In one case dissolution rates were higher for P-D-L and D-L-P mixes than for the corresponding P-L-D

Fig. 3.22 The influence of mixing sequence on the dissolution profile of phenytoin sodium capsules containing lactose D_1 as diluent and 0.5% magnesium stearate as lubricant

◇ P-D; ■ P-D-L; ▲ D-L-P; ● P-L-D

(a) 80% DILUENT



(b) 95% DILUENT

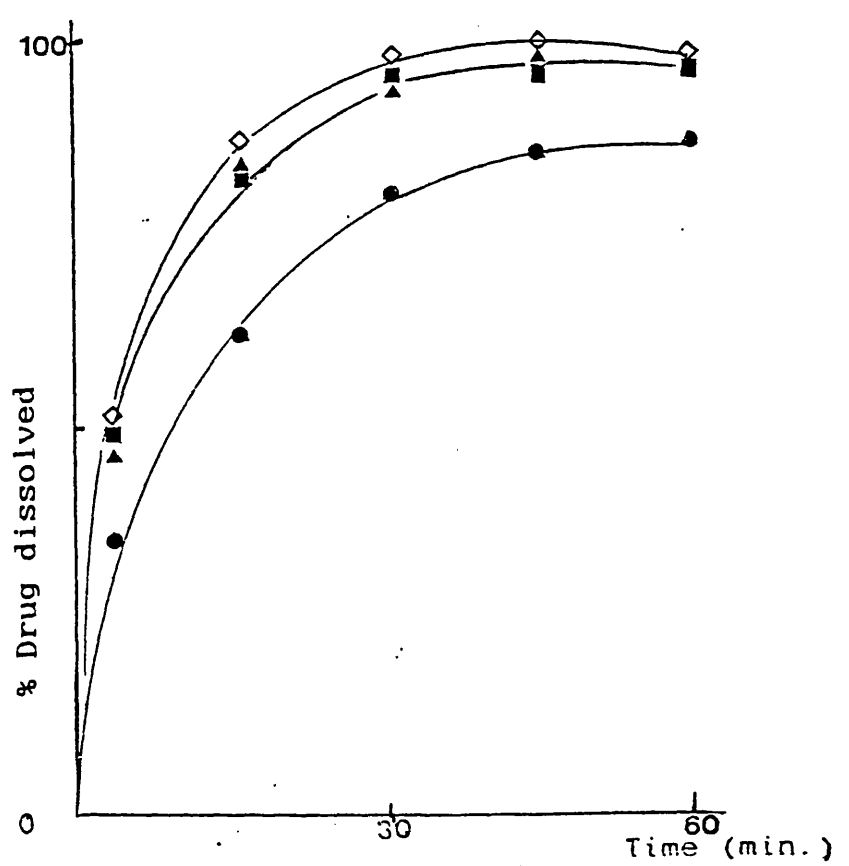


Fig. 3.23 The influence of mixing sequence on the dissolution profile of phenytoin sodium capsules containing lactose D_2 as diluent and 0.5% magnesium stearate as lubricant

◇ P-D; ■ P-D-L; ▲ D-L-P; ● P-L-D

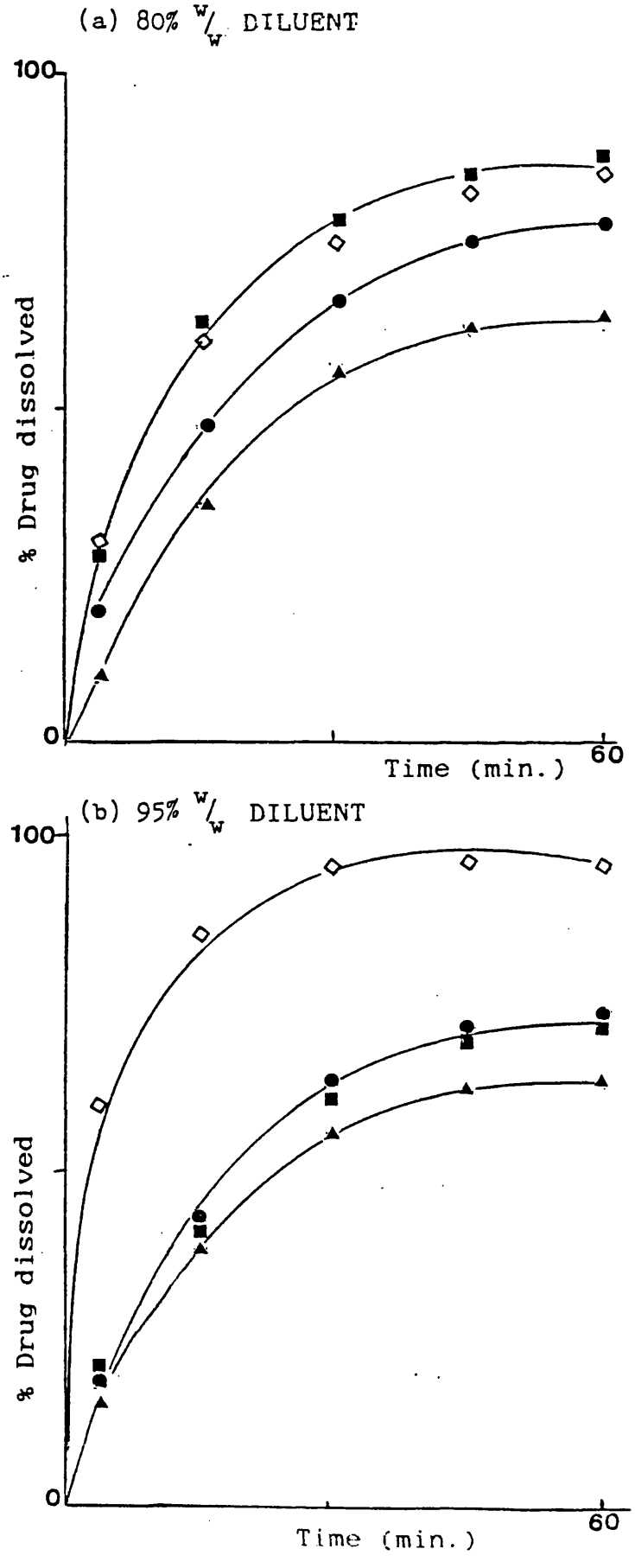
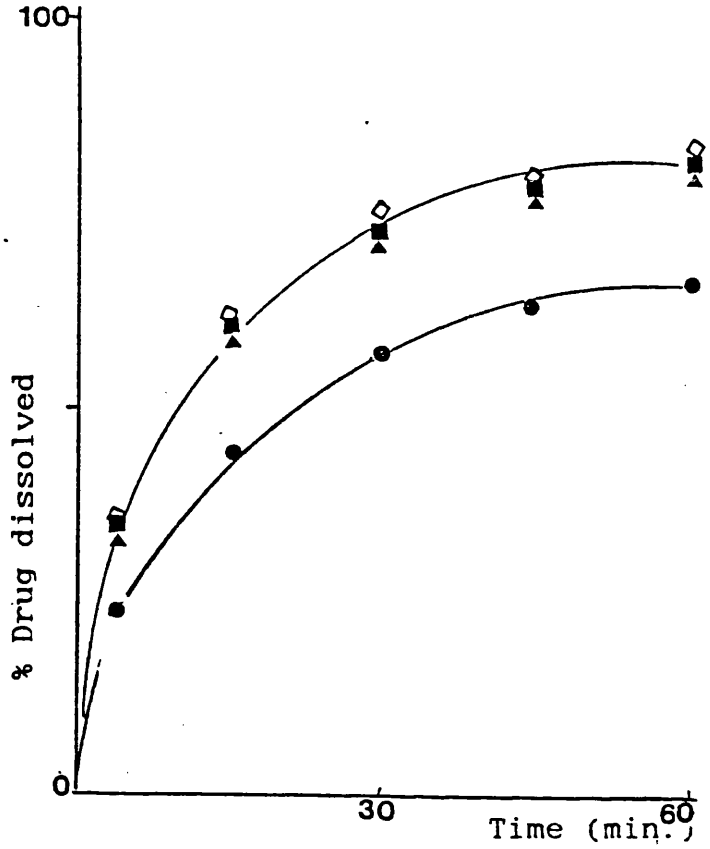


Fig. 3.24 The influence of mixing sequence on the dissolution of phenytoin sodium capsules containing calcium sulphate D_4 as diluent and 0.5% magnesium stearate as lubricant

◇ P-D; ■ P-D-L; ▲ D-L-P; ● P-L-D

(a) 80% $^{W}/_{W}$ DILUENT



(b) 95% $^{W}/_{W}$ DILUENT

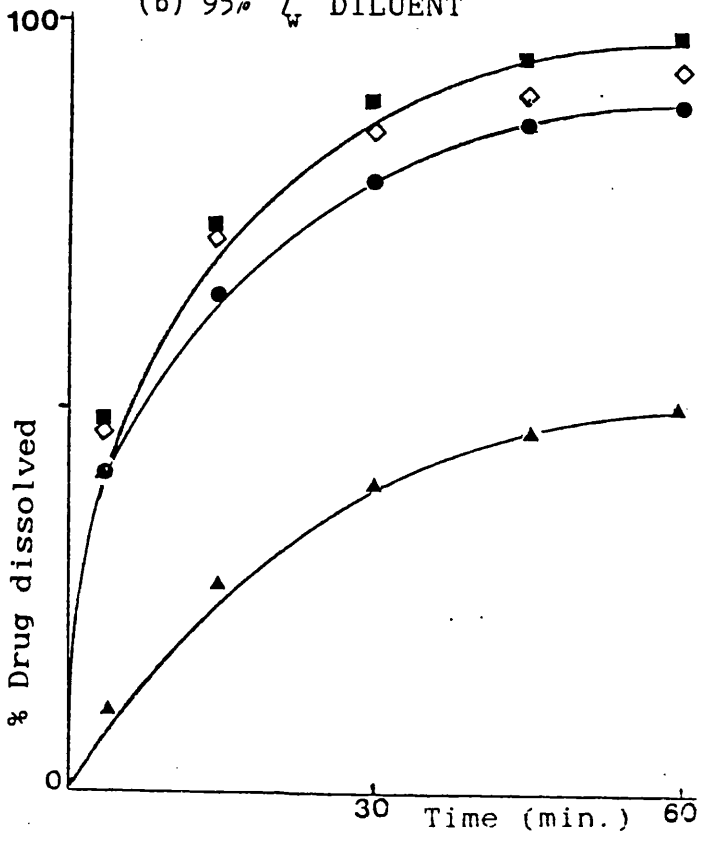


Fig. 3.25 The influence of diluent type and concentration on the percentage of phenytoin sodium dissolved in 30 minutes (W_{30})
Lubricant concentration 0.5% $^{w}/_{w}$; mixing sequence ◇ P-D; ▲ D-L-P.

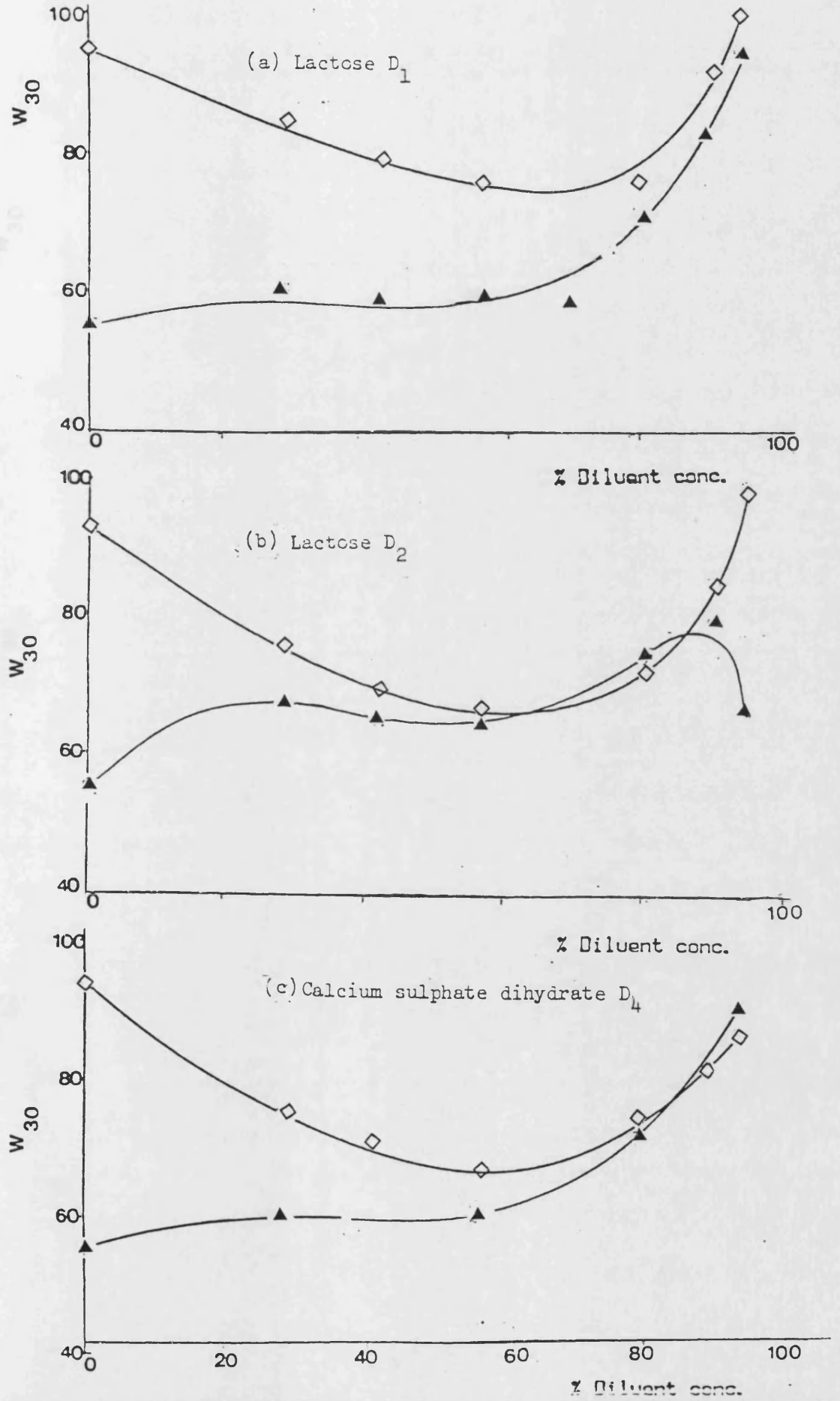


Fig. 3.26 The influence of diluent type and concentration on the percentage of phenytoin Na dissolved in 30 minutes (W_{30}). Lubricant concentration 0.5% $^{w}/_{w}$; mixing sequence ◇ P-D; ● P-L-D

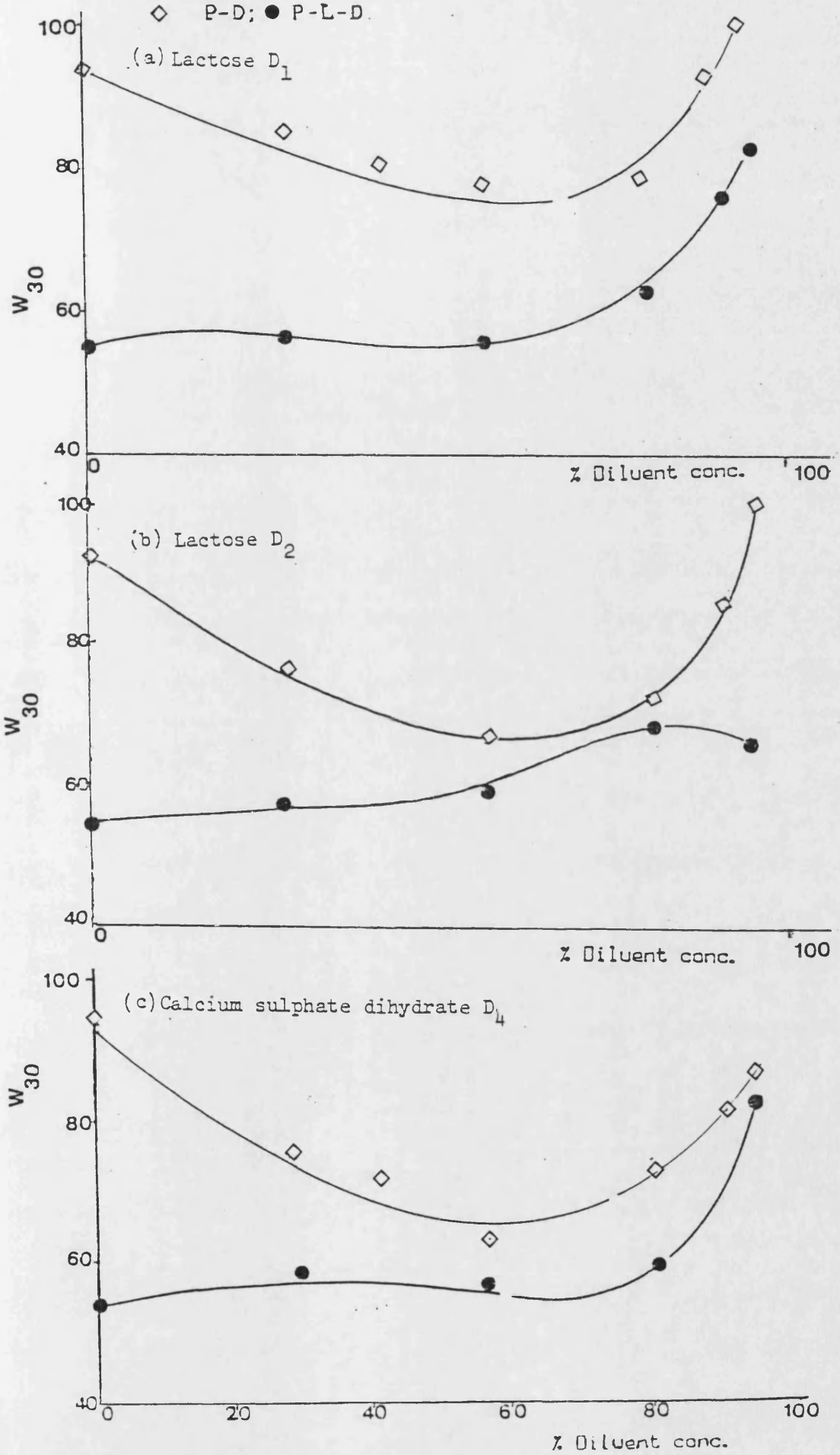
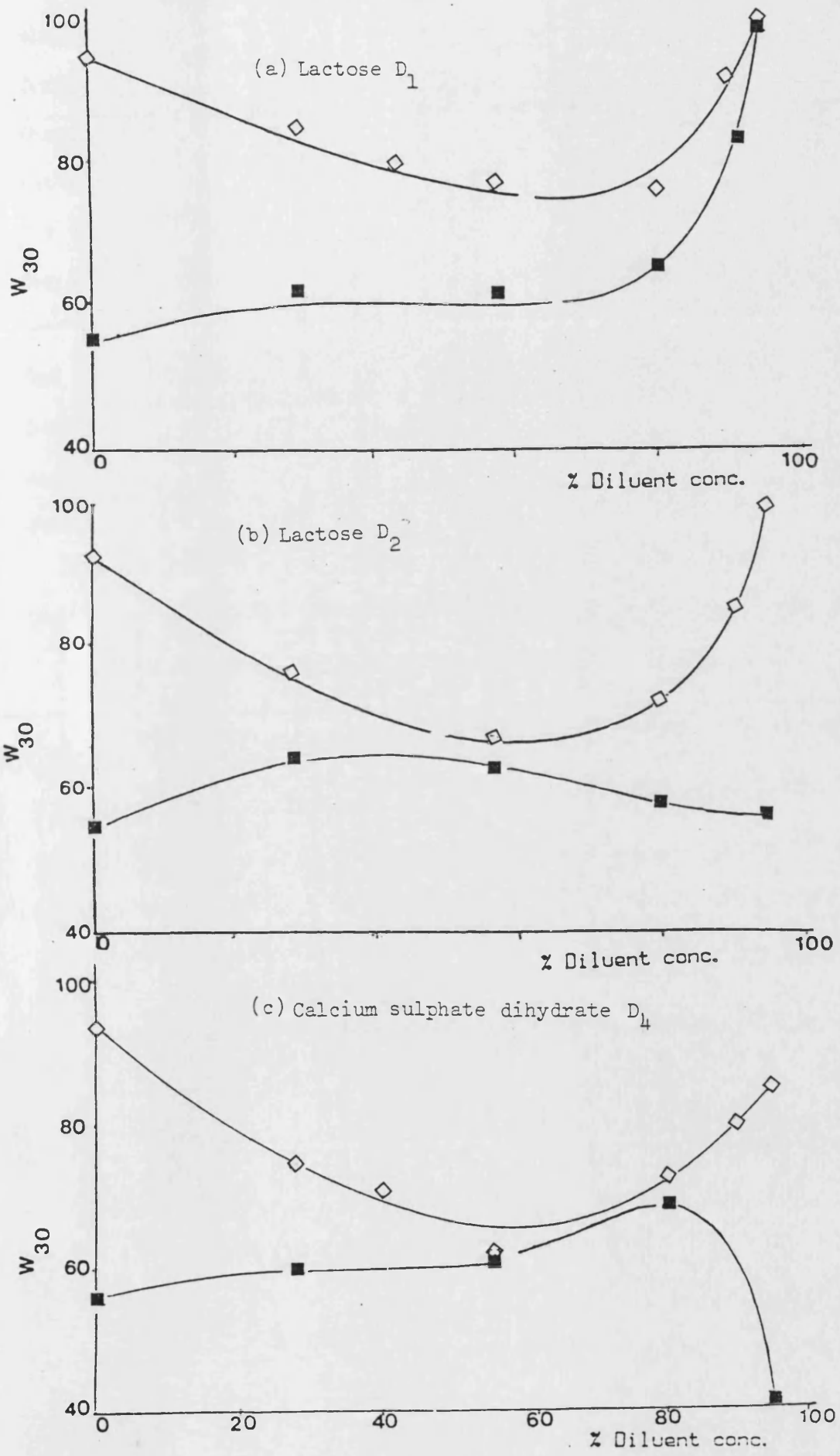


Fig. 3.27 The influence of diluent type and concentration on the percentage of phenytoin sodium dissolved in 30 minutes (W_{30}). Lubricant concentration 0.5% $^{w}/_{w}$; mixing sequence ◇ P-D; ■ P-D-L.



mixing sequence. This was observed for 80% or 95% $^{w}/_{w}$ lactose D_1 formulations (Fig. 3.22a and b) and 80% calcium sulphate D_4 formulations (Fig. 3.24a). In the second pattern, the dissolution rates followed the order P-D-L $\geqslant$ P-L-D $>$ D-L-P; and was observed for 80 or 95% lactose D_2 formulations (Fig. 3.23a and b) and also for 95% calcium sulphate D_4 formulations (Fig. 3.23b). The overall pattern is clearer when the plots of W_{30} versus diluent concentration for the different mixing sequences are examined (Fig. 3.25, 3.26 and 3.27). To appreciate the meaning of these, it is necessary to understand the spatial distribution of the components in the total mix. These results are therefore discussed in Section 3.5.

3.3 DISSOLUTION OF PHENYTOIN SODIUM CAPSULES: THE INFLUENCE OF RELATIVE HUMIDITY AND PROLONGED STORAGE

The values for percentage moisture gain in capsule formulations stored at 0, 55 and 86% RH are shown in Table 3.10. With an increase in Relative Humidity, the moisture sorption into capsules increased. Capsule formulations containing lactose showed higher moisture gain at 86% RH after 8 weeks of storage than those of calcium sulphate. The dissolution of lactose particles on uptake of moisture probably facilitates further absorption of moisture.

The influence of storage at different Relative Humidity on the percentage of phenytoin sodium dissolved in 30 minutes, W_{30}, is shown in Fig. 3.28 for drug alone and in Fig. 3.29 for two-component formulations. Dissolution from capsules containing drug alone was not significantly influenced by prolonged storage at 0% RH (Fig. 3.28a). At higher levels of 55 and 86% RH, capsule dissolution of single

Table 3.10 % Change in moisture content of capsule formulations stored for up to 8 weeks at 0, 55 and 86% Relative Humidity

Capsule	% RH	% loss or gain in moisture			
		1 wk	2 wks	4 wks	8 wks
empty capsule	0	-12.2	-11.6	-11.1	-10.8
	55	+ 0.8	+ 1.2	+ 1.2	+ 1.2
	86	+10.8	+14.5	+15.0	+15.9
0.200g phenytoin sodium capsule	0	- 3.3	- 3.4	- 3.4	- 3.3
	55	+10.0	+10.6	+13.7	+15.7
	86	+23.1	+23.0	+23.4	+24.9
0.200g phenytoin sodium capsule containing 56.5% lactose D_1	0	- 3.1	- 3.0	- 3.1	- 3.0
	55	+ 5.1	+ 5.5	+ 7.0	+ 7.4
	86	+11.1	+14.0	+17.0	+23.8
0.200g phenytoin sodium capsule containing 56.5% $CaSO_4.2H_2O$ D_4	0	- 3.2	- 3.1	- 3.2	- 3.1
	55	+ 5.3	+ 5.6	+ 7.4	+ 7.7
	86	+12.0	+13.3	+16.0	+16.9

Fig. 3.28 The influence of prolonged storage under different Relative Humidities on dissolution from capsules containing 200mg phenytoin sodium

(a) 0% RH; (b) 55% RH, and (c) 86% RH

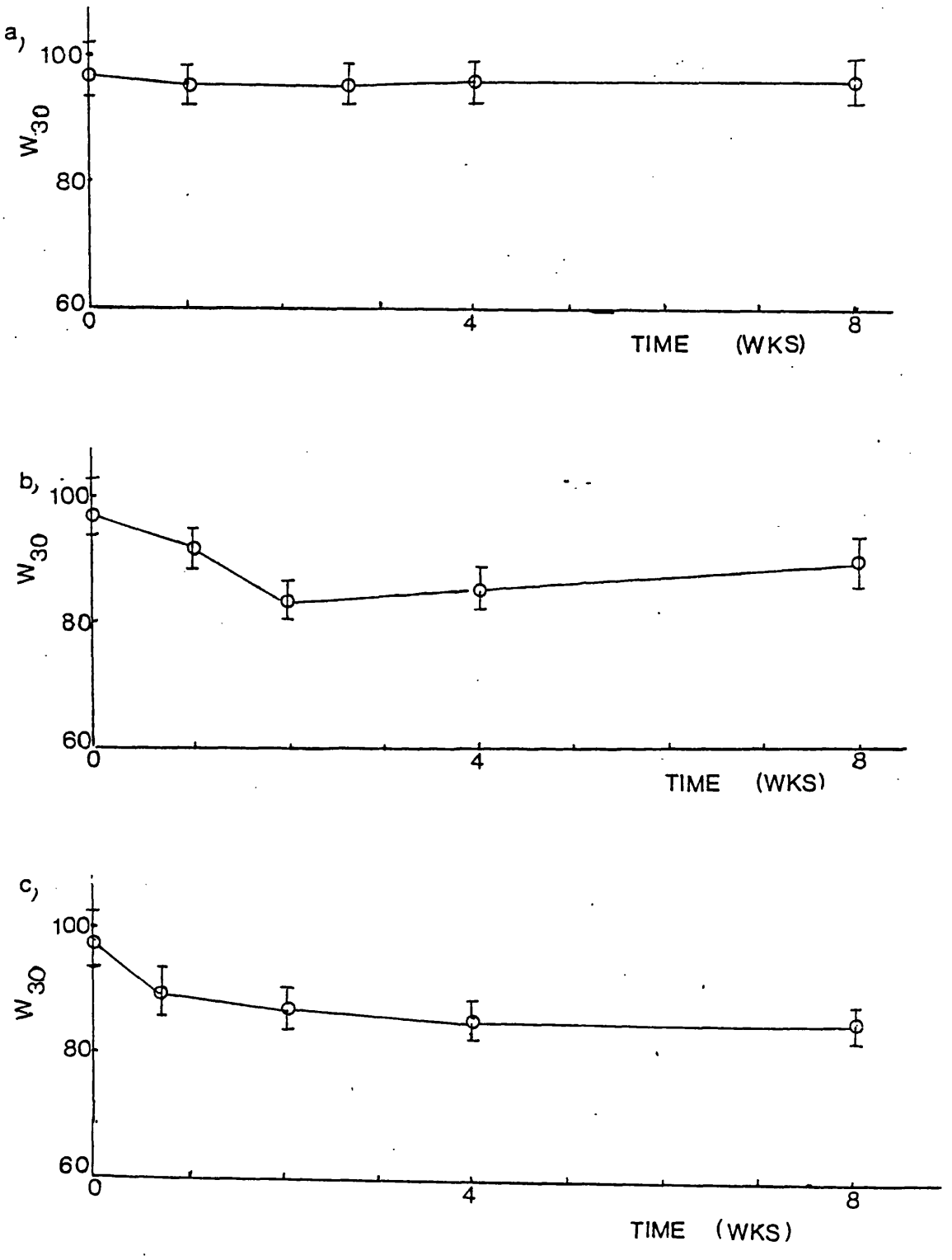
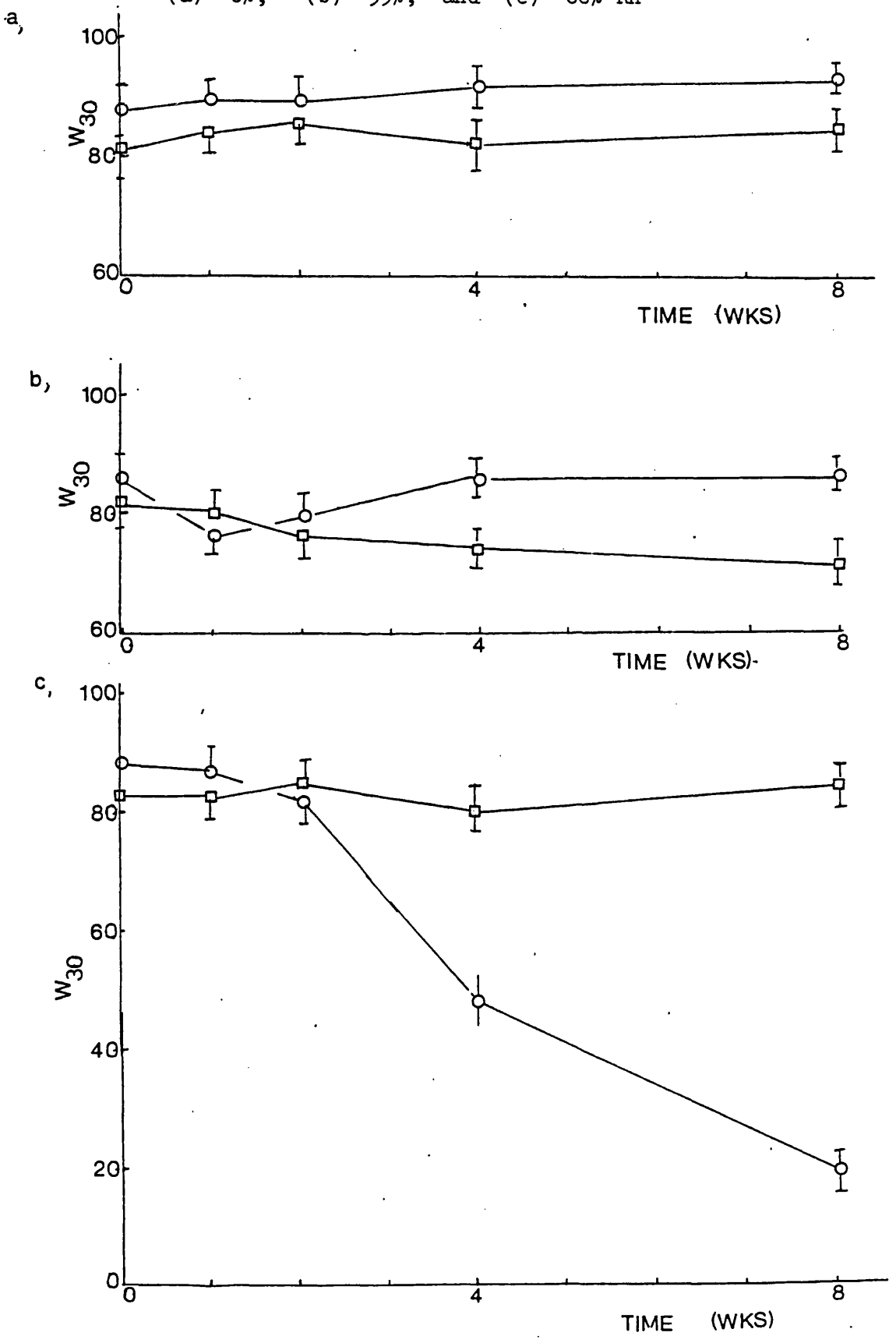


Fig. 3.29 The influence of prolonged storage under different Relative Humidities on dissolution from capsules containing 56.5% diluent

○ lactose, □ calcium sulphate

(a) 0%; (b) 55%, and (c) 86% RH

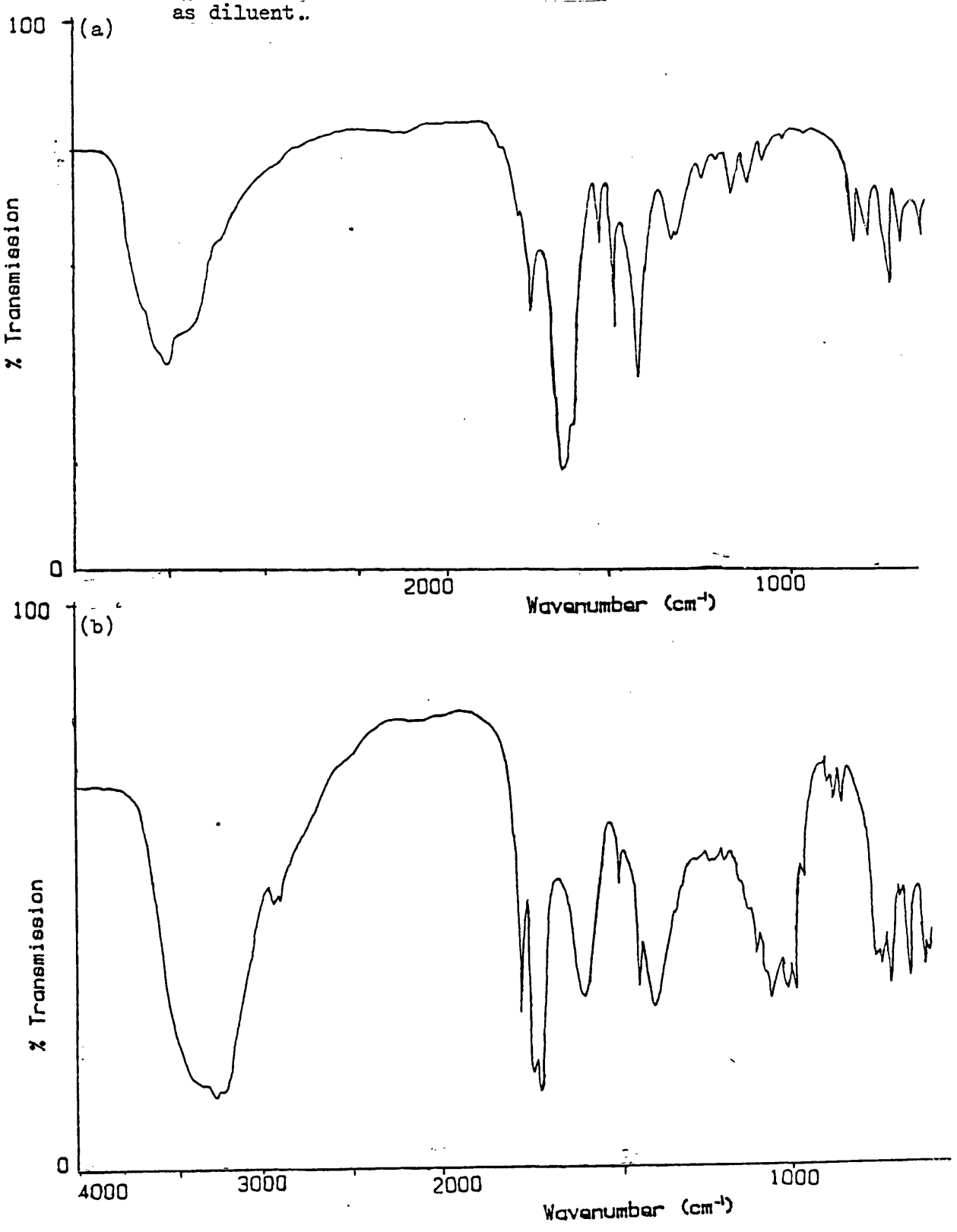


component formulations was retarded after prolonged storage (Fig. 3.28b and c). There was no significant difference in release rates between capsule formulations stored under either 55 or 86% RH. For two-component formulations, there was no significant effect on dissolution when capsules were stored for 8 weeks at 0% RH (Fig. 3.29a). Under 55% RH, the dissolution rate from formulations of lactose was initially reduced after 1 to 2 weeks of storage. After further storage, for 4 to 8 weeks, dissolution rates were comparable to capsule formulations tested immediately after preparation. Capsules of calcium sulphate showed a gradual reduction in dissolution rate on prolonged storage at 55% RH. Under 86% RH, the dissolution rate of lactose formulations was greatly retarded during storage. Capsules tested after 8 weeks of storage released only 20% of the drug in 30 minutes, as compared to 88% when the formulations were tested immediately after preparation. Figure 3.30 shows IR spectra of capsule contents after 8 weeks of storage at 86% RH. Fig. 3.30a is for phenytoin sodium filled into capsules as a single-component drug formulation and Fig. 3.30b for a two-component formulation containing phenytoin sodium with lactose as diluent. In both cases, it is obvious that the acid form, phenytoin, has been produced due to the appearance of characteristic peaks at 1770, 1750 and 1720 cm^{-1} (refer Fig. 3.2b). Therefore the retardation in dissolution observed for capsule formulations (86% RH) is due to the partial conversion of the sodium salt to the insoluble and relatively hydrophobic phenytoin. For capsule formulations containing lactose most of the drug appears to have been converted to phenytoin (Fig. 3.30b). This effect, combined with the partial dissolution of lactose particles in the capsule under conditions of high RH explains why the rate of dissolution of drug from such capsules was greatly retarded. In contrast

Fig. 3.30 Infra-red spectra of capsule contents after 8 weeks of storage at 86% RH

(a) capsule containing only Phenytoin sodium

(b) capsule containing phenytoin sodium with 56.5% lactose as diluent.



for formulations containing calcium sulphate very little dissolution of diluent occurs, any phenytoin which is precipitated is also in contact with the diluent and the effect of storage under high RH is minimal. Formulations containing lactose showed brown discolouration after 4 weeks of storage. This effect is due to the alkaline hydrolysis of lactose, a reaction common to reducing sugars (Browne, 1955).

3.4 CHARACTERISATION OF POWDER MIXES BY SEM COMBINED WITH X-RAY ANALYSIS

3.4.1 Spatial distribution of particles in two-component mixes

3.4.1.1 Drug-diluent mixes

Figure 3.31 shows the effect of increasing the proportion of phenytoin sodium in a drug-diluent mix on the p/b ratio of Na^+ detected on the diluent surface. The diluents were lactose D_1, lactose D_2 and calcium sulphate dihydrate D_4. The results show no significant change in the phenytoin sodium concentration on the diluent surface when the total drug concentration is increased from 5 to 30%. It can be assumed therefore that the diluent surfaces were fully saturated in a powder mix containing 5% drug. Fig. 3.32 shows photomicrographs of binary mixes of 5% phenytoin sodium with lactose D_1 (Graph a) and calcium sulphate D_4 (Graph b). Each mix may be described as a partially ordered random mix. A close examination of a lactose particle under higher magnification (Fig. 3.32c) show that although there was a noticeable amount of free drug visible in photomicrograph (a), there was not complete coverage of the diluent surface. There appear to be sites of preferential adhesion where multilayers of drug adhere to the diluent surface. The amount of drug present on the diluent surface as indicated by p/b ratios followed the sequence $D_2 > D_1 > D_4$.

The number of fine particles of phenytoin sodium which a single diluent particle theoretically is capable of carrying in a closed packed monolayer, was calculated from Equation 1.21 (page 42). The results

Fig. 3.31 The influence of phenytoin sodium concentrations on p/b ratio for Na^+ detected on diluent surface

● lactose D_1; ▲ lactose D_2; ■ calcium sulphate dihydrate D_4

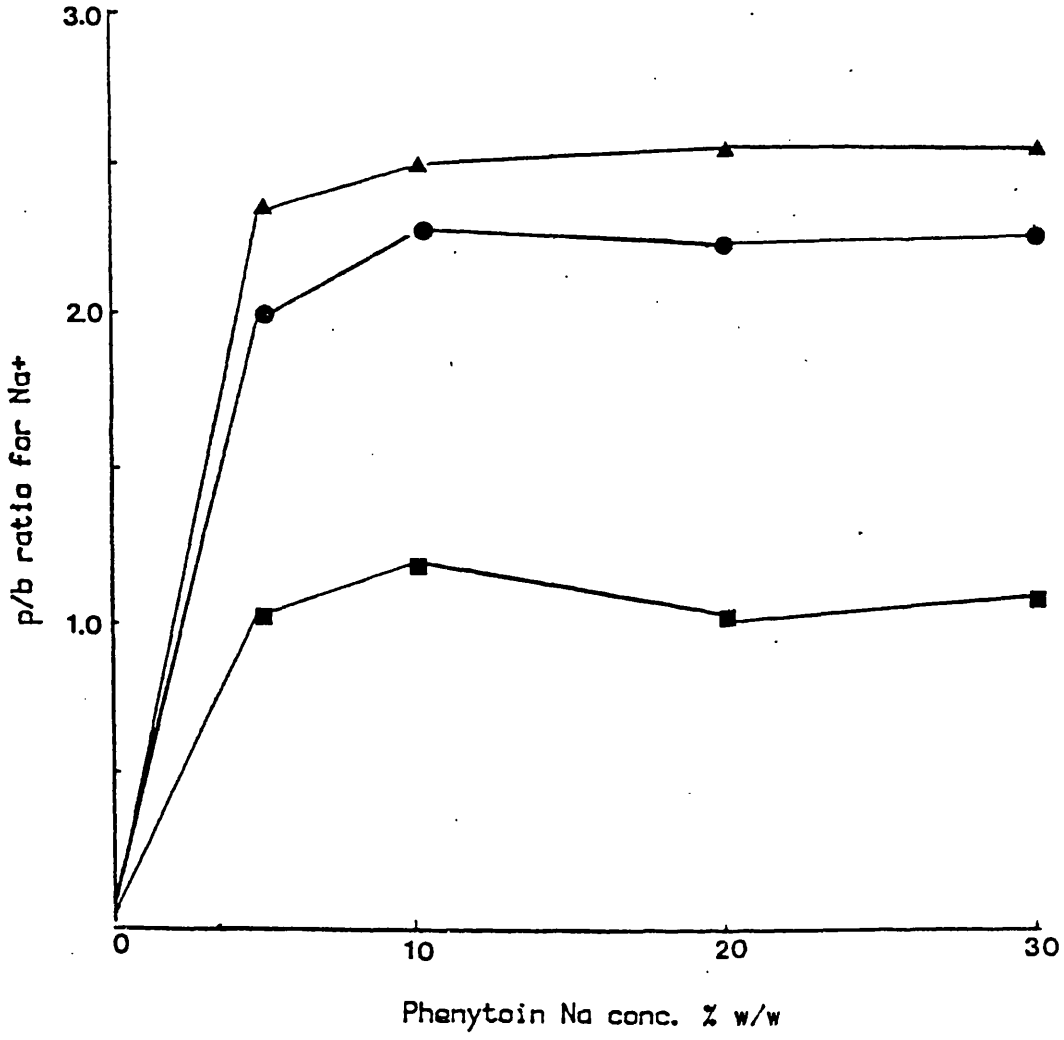
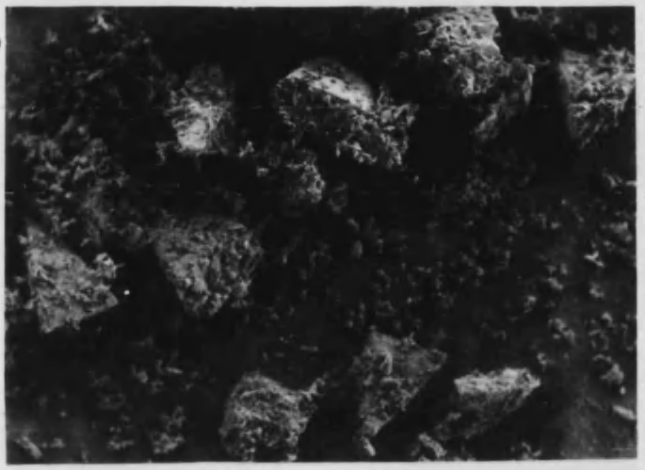


Fig 3.32 Photomicrographs of
a) Binary mix of 5% Phenytoin Na and lactose D_1.
b) Binary mix of 5% Phenytoin Na and Ca sulphate D_4.
c) Ordered unit of Phenytoin Na-lactose D_1.

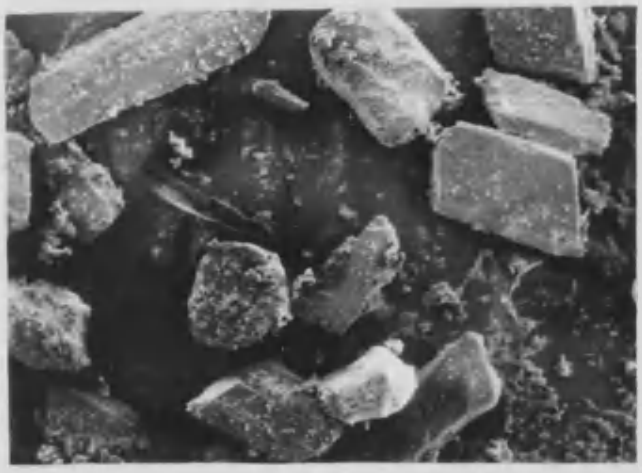
a)



x 40

1000 µm

b)



x 40

1000 µm

c)

x 200

100 µm

are shown in Table 3.11. In each case the theoretical saturation number of drug particles on diluent surface is 21,831.

Table 3.11 Theoretical number of fine particles, N°, on each coarse diluent particle at different concentrations of phenytoin sodium

($f' = 1$)

% drug content	Lactose D_1 N°	Lactose D_2 N°	Calcium sulphate D_4 N°
0.5	2,482	2,452	3,708
1.0	5,489	4,929	7,455
5.0	26,000	25,684	38,842
10.0	54,889	54,222	82,000

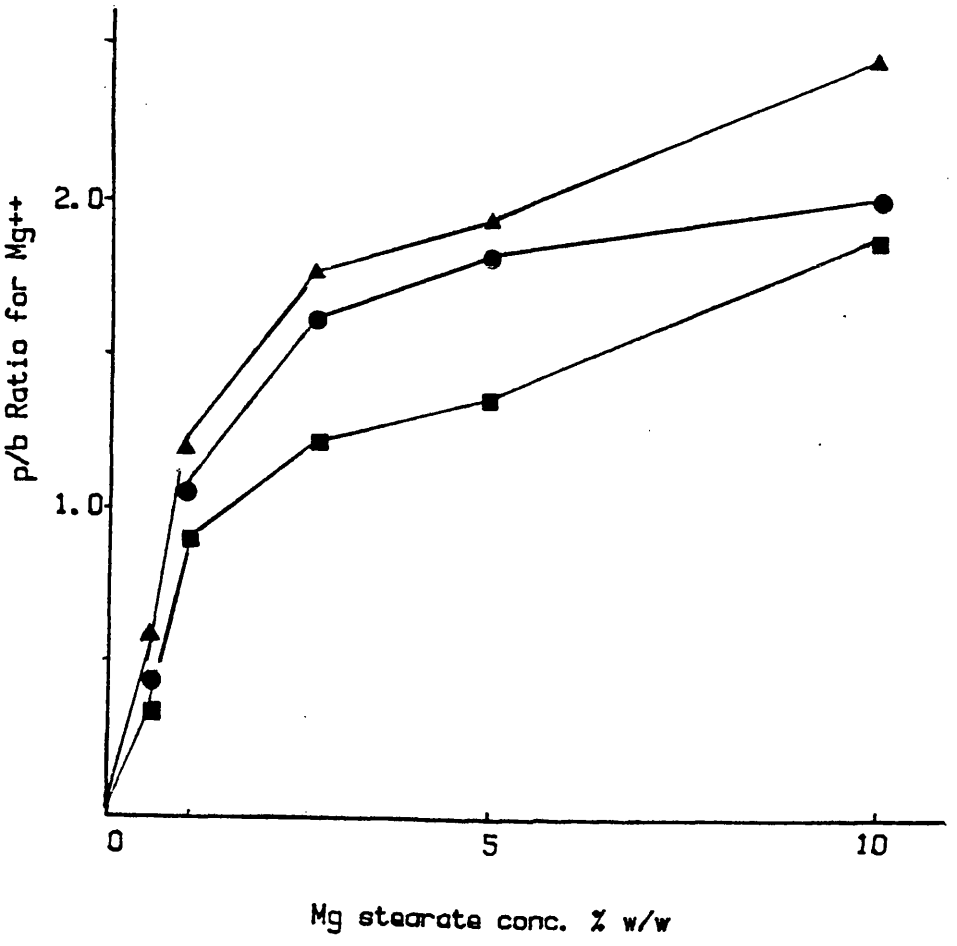
Assuming all the drug particles were capable of adhering to the surface of the diluent particles, the concentration of phenytoin sodium required to saturate the surfaces of lactose D_1, D_2 and calcium sulphate D_4 in a monolayer would be 4.2, 4.3 and 2.9% respectively. It is therefore not surprising that at concentrations higher than these (5-30%), the diluent surfaces appeared to be fully saturated.

3.4.1.2 Lubricant-diluent mixes

The results showing the effect of adding increasing concentrations of magnesium stearate on the p/b ratio for Mg^{2+} detected on the surface of diluents D_1, D_2 and D_4 are shown in Fig. 3.33. There were higher levels of magnesium stearate present on lactose D_2 surface than on lactose D_1 or calcium sulphate D_4. At lubricant levels up to 1%, there is an

Fig. 3.33 The influence of magnesium stearate concentrations on p/b ratios of Mg^{2+} detected in diluent surface

● lactose D_1; ▲ lactose D_2; ■ calcium sulphate D_4



approximately linear relationship between the concentration of added lubricant and the amount of lubricant adhering to the diluent surface. Above 1%, lubricant levels on the lactose D_1 surface appeared to approach a limiting value indicating that the surface was almost saturated. Fig. 3.34a shows a photomicrograph of a mix containing diluent D_1 with 1% lubricant and Fig. 3.34b shows the same surface at higher magnification. The entire diluent surface did not appear saturated although certain regions (bottom left hand corner of Fig. 3.34a) appear saturated with multilayer adhesion of lubricant. Figure 3.34c shows a photomicrograph of a mix of lactose D_1 with 5% lubricant. The lubricant particles seem to have formed a film over most of the substrate surface.

The number of particles of magnesium stearate each diluent is capable of carrying in a monolayer at lubricant levels of 0.5 to 10% is shown in Table 3.12. In each case the theoretical number of particles required to saturate the diluent surface is 58,000.

Table 3.12 Theoretical number of magnesium stearate particles, N°, on each coarse diluent particle at different lubricant concentrations

Concentration of lubricant (%)	Lactose D_1 N°	Lactose D_2 N°	Calcium sulphate D_4 N°
0.5	14,486	14,298	21,634
1.0	29,119	28,746	43,487
2.5	73,917	72,957	110,390
5.0	151,720	149,748	226,583
10.0	320,030	316,142	478,309

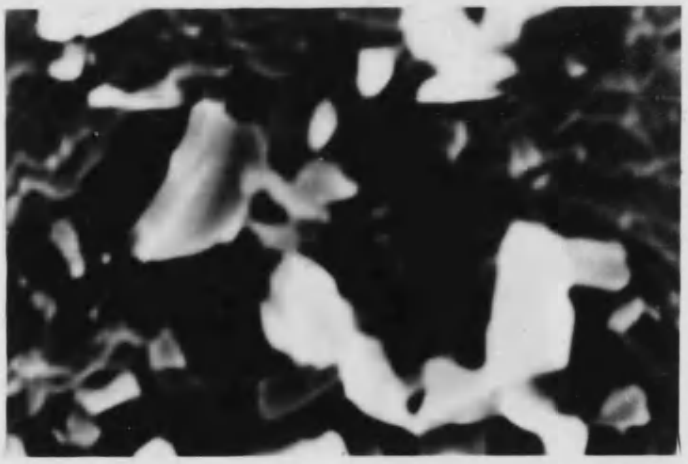
Fig 3.34 Photomicrographs showing binary mixes of
a) 1% Mg. stearate and lactose D_1.
b) 1% Mg. stearate and lactose D_1 at higher magnification.
c) 5% Mg. stearate and lactose D_1.

a)

x 600

10 µm

b)



x 6000

1.0 µm

c)

x 600

10 µm

Assuming that all adhesion sites on the coarse diluent surface were active sites, approximately 2% of added lubricant would saturate the surfaces of lactose particles D_1 and D_2, and about 1.3% would saturate the calcium sulphate surface. The fact that the results (Fig. 3.33) show increased adhesion of lubricant beyond these levels would suggest that multilayer adhesion had occurred. Because of the cohesive nature of magnesium stearate particles it is envisaged that lubricant may adhere on lubricant particles already present on diluent surface.

3.4.1.3 Lubricant-drug mixes

Magnesium stearate also forms a lubricant film on phenytoin sodium particles. Fig. 3.35a shows a photomicrograph of a needle-shaped drug particle with adhering fine particles. Fig. 3.35b and c show X-ray mapping of Na^{2+} and Mg^{2+} respectively for the same field of view. Lubricant particles are seen adhering to the phenytoin sodium particle. Coverage is not uniform and there appear to be sites of preferential adhesion. The amount of lubricant present in the mix (5%) is in excess of that required to saturate the drug surface. Therefore it is expected that a binary mix of drug with 5% magnesium stearate will be a partially ordered random mix.

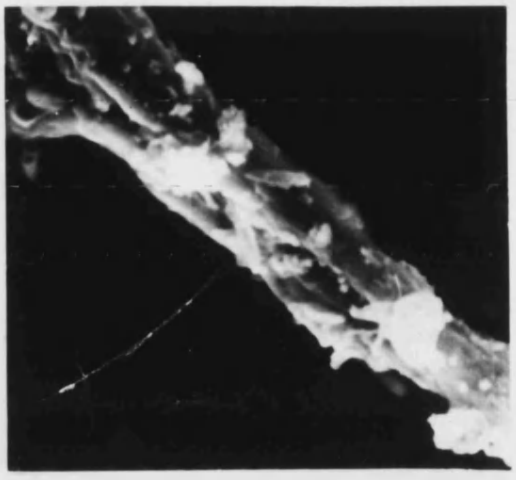
3.4.2 Spatial distribution of components in three-component mixes

3.4.2.1 Effect of lubricant concentration

Increasing amounts of magnesium stearate were added to binary drug-diluent mixes, the resulting p/b ratios for Na^+ and Mg^{2+} on the diluent surface are shown in Table 3.13 and in Fig. 3.36a for lactose D_1, Fig. 3.36b for calcium sulphate D_4 and Fig. 3.36c for lactose D_2.

Fig 3.35 Photomicrographs of
a) Ordered unit of Mg. stearate-Phenytoin sodium in a powder mix containing 5% lubricant.
b) X-ray dot mapping for **Na**. ion.
c) X-ray dot mapping for **Mg**. ion.

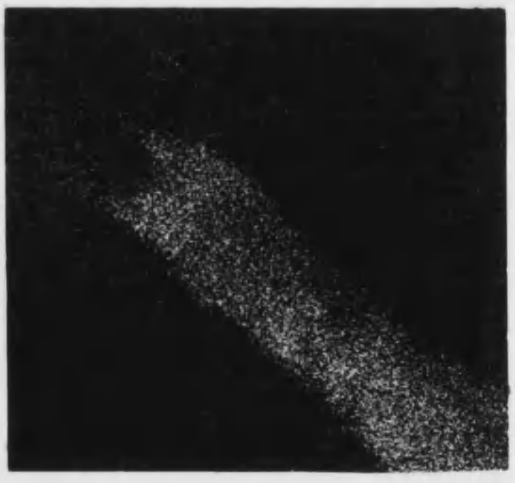
a)



x 1800

10 µm

b)



10 µm

c)

10 µm

Table 3.13 p/b ratios of Na^+ and Mg^{2+} on diluent surface of powder mixes containing varying concentrations of lubricant

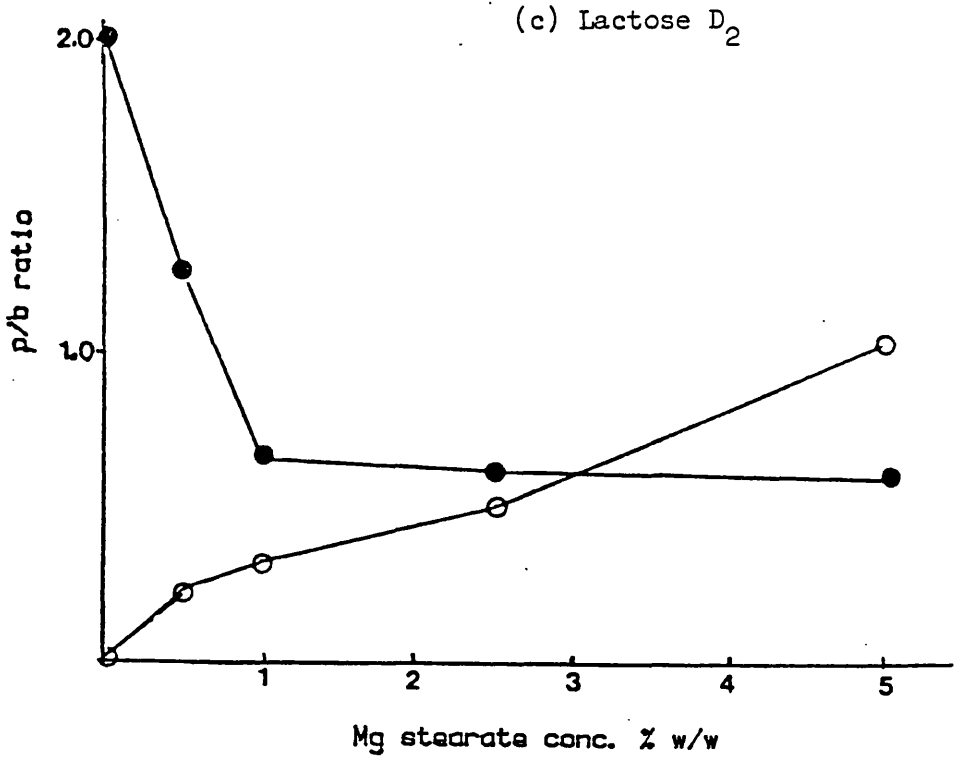
(values in brackets refer to standard deviation)

Mix	Lubricant conc % w/w	Diluent					
		Lactose D_1		Lactose D_2		Calcium sulphate D_4	
		Na^+	Mg^{2+}	Na^+	Mg^{2+}	Na^+	Mg^{2+}
P-$D_{95\%}$	0	2.00 (0.40)	0.07 (0.05)	2.35 (0.52)	0.10 (0.05)	1.08 (0.35)	0.07 (0.04)
P-D-L	0.5	1.25 (0.32)	0.23 (0.16)	3.39 (0.65)	0.39 (0.08)	0.74 (0.29)	0.18 (0.07)
	1.0	0.67 (0.16)	0.31 (0.05)	1.55 (0.58)	0.48 (0.13)	0.66 (0.19)	0.41 (0.08)
	2.5	0.63 (0.15)	0.51 (0.12)	1.03 (0.45)	0.75 (0.20)	0.45 (0.12)	0.49 (0.09)
	5.0	0.61 (0.14)	1.05 (0.17)	0.82 (0.15)	1.42 (0.34)	0.48 (0.17)	0.74 (0.20)
D-L	5.0	-	1.88 (0.29)	-	1.92 (0.38)	-	1.40 (0.52)

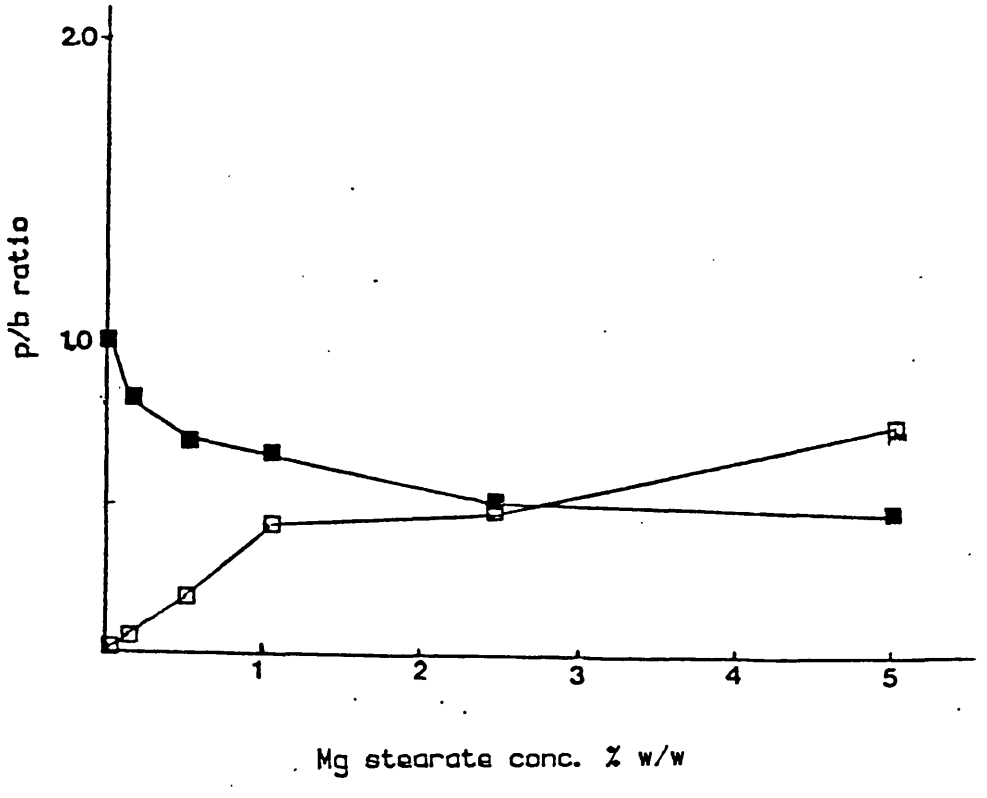
Fig 3.36 p/b ratios of Na^+ (closed symbols) and Mg^{2+} (open symbols) showing the effect of adding increasing concentrations of magnesium stearate (L_1) to a binary mix of drug and diluent (1:19)

(a) Lactose D_1 (b) calcium sulphate dihydrate D_4 (c) Lactose D_2

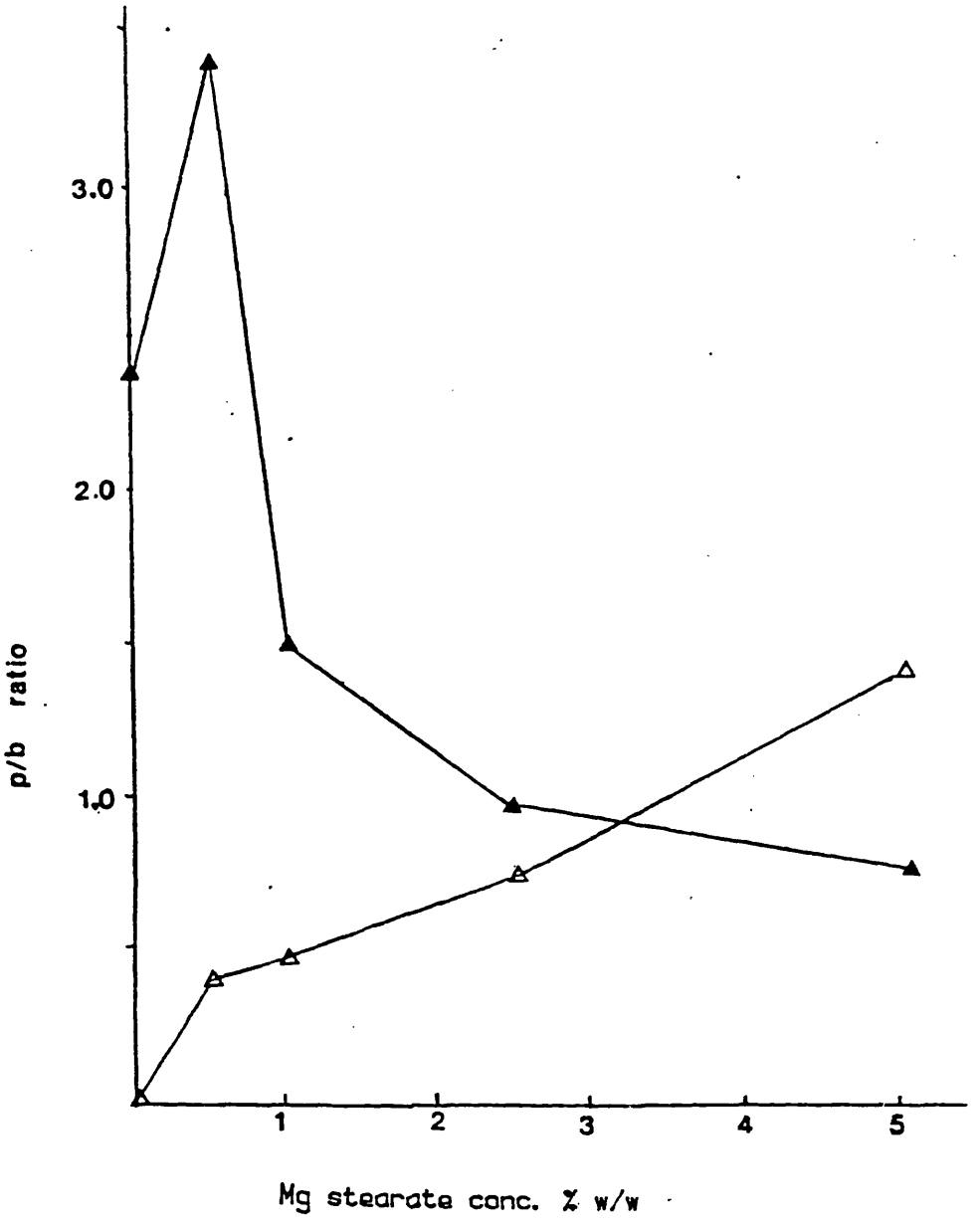
(a)



(b)



(c)



There is a gradual reduction in concentration of drug adhering to the diluent surface. At the same time, there is increased adhesion of lubricant to the diluent. When 5% lubricant is added to lactose D_1, D_2 or calcium sulphate D_4, there is a reduction in the amount of adhering drug to about 31, 35 and 44% respectively of the initial values obtained in P-D mixes. The results also show a preferential adhesion of magnesium stearate to lactose as compared to calcium sulphate particles. The gradual reduction in drug concentration on the diluent surfaces is explained by competition between drug and lubricant particles for adhesion sites on the diluent with lubricant particles displacing drug. The residual concentration of drug remaining (30-45%), in mixes containing 5% lubricant, may be due to drug particles which have formed strong adhesional bonds with diluent and could not be dislodged by the competing effect of the magnesium stearate. Such drug particles may be lodged in crevices where they can form a strong adhesive couple on the diluent surface (Staniforth, 1980). Another possibility is that drug particles may associate with lubricant particles to form stable drug-lubricant units on the diluent surface. Table 3.14 compares the effects of adding 0.5% magnesium stearate to binary mixes of drug and diluent containing different amounts of diluent. The two types of lactose, D_1 and D_2, are compared.

Lactose D_1 showed a fall in drug concentration when 0.5% lubricant was added, however, for lactose D_2 the drug concentrations were always increased. Two mechanisms may be proposed to explain the unexpected result with lactose D_2; these are shown schematically in Fig. 3.37. The first possibility (Scheme 1) is that the magnesium stearate adheres to the diluent surface enabling more drug particles to adhere either to lubricant particles on the diluent surface or possibly

Fig. 3.37 Two possible mechanisms proposed to explain the increased adhesion of phenytoin sodium present on diluent D_2 surface when 0.5% magnesium stearate is added to a binary mix of drug and diluent

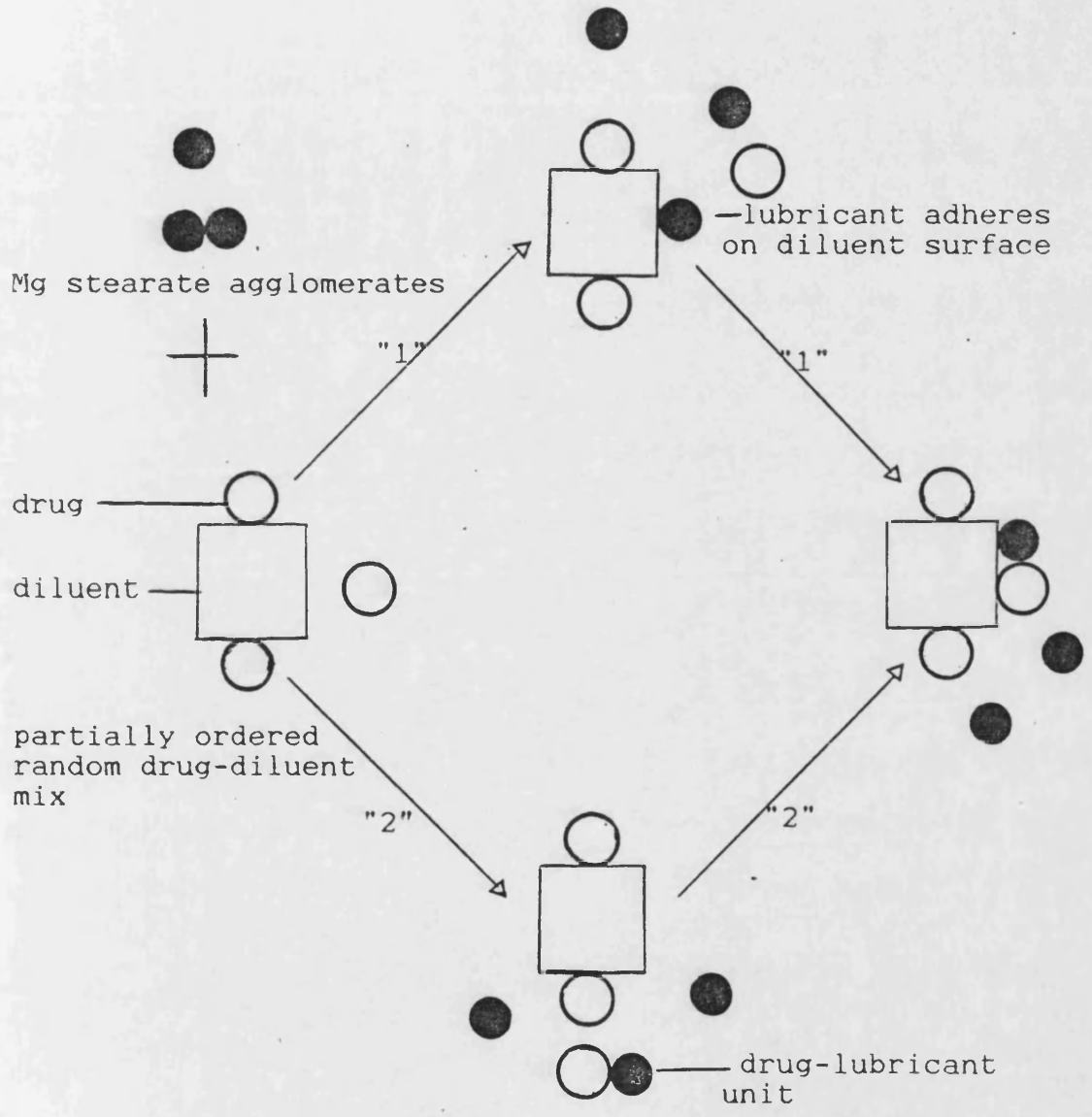


Table 3.14 p/b ratios of Na^+ and Mg^{2+} on diluent surface in powder mixes containing phenytoin sodium and lactose D_1 and D_2 as diluent to which 0.5% magnesium stearate has been added

(values in brackets refer to standard deviation)

Lactose conc. %	Mix	Lactose D_1		Lactose D_2	
		Na^+	Mg^{2+}	Na^+	Mg^{2+}
80	P-D	2.27 (0.67)	0.12 (0.03)	2.59 (0.52)	0.18 (0.08)
	P-D-L	2.04 (0.94)	0.16 (0.08)	3.61 (1.12)	0.37 (0.05)
90	P-D	2.31 (0.51)	0.08 (0.04)	2.44 (0.51)	0.14 (0.04)
	P-D-L	1.53 (0.52)	0.19 (0.07)	3.45 (0.85)	0.41 (0.08)
95	P-D	2.00 (0.40)	0.07 (0.05)	2.35 (0.52)	0.10 (0.05)
	P-D-L	1.25 (0.32)	0.23 (0.16)	3.39 (0.65)	0.39 (0.08)

to the diluent surface adjacent to lubricant particles. The second possibility (Scheme 2) is that lubricant particles interact with free drug particles forming drug-lubricant units which then adhere to the diluent surface. It is likely that both mechanisms do occur during the mixing process although one process may predominate. However, such units formed on the diluent surface appear to be unstable as they are easily dislodged by adding increasing concentrations of magnesium stearate. Probably this explains why there is no evidence for such units in mixes containing lactose D_1 or calcium sulphate D_4.

In terms of the spatial structure of the whole mix as increasing amounts of drug are stripped from diluent surface by the lubricant, the levels of free drug available to interact with ordered units within the mix will increase. This free drug will interact with lubricant particles in such a way that the total mix will contain drug-diluent-lubricant units, drug-lubricant units and probably also free agglomerates of lubricants.

3.4.2.2 Effect of mixing sequence

The effect of mixing sequence on p/b ratios of Na^+ and Mg^{2+} detected on diluent surfaces are shown in Table 3.15 and Fig. 3.38. An analysis of variance of the effect of mixing sequence indicates that the mixing sequence had a significant effect on levels of phenytoin sodium and magnesium stearate detected on the diluent surface. There was also a significant interaction between mixing sequence and the type of diluent used (Table 3.16 and 3.17).

From Fig. 3.38 when diluent was first mixed with lubricant in the D-L-P sequence, the adhesion of drug and lubricant was more extensive than in the P-L-D sequence. In P-D-L mixes, the levels of lubricant on the diluent surface were similar to those in D-L-P mixes but the quantity of phenytoin sodium adhering depended on whether the lubricant impaired adhesion or facilitated adhesion of drug. Where as in the case of lactose D_1 and calcium sulphate D_4, the lubricant presence impaired adhesion, the concentration of drug on the diluent surface was lower than for the other two mixing sequences. When the lubricant facilitated adhesion of drug, as in the case of D_2, drug concentrations were higher.

In the D-L-P mixes, the amount of lubricant detected on the surface of diluent D_1 was 64%, D_2 was 70% and D_4 was 51% of the figure recorded for the original D-$L_{0.5\%}$ mix (Table 3.15). From Equation 1.21 (page 42), about 2% lubricant is required to fully saturate the diluent surface, therefore assuming that when 0.5% magnesium stearate was added, all lubricant adhered to the diluent surface, these results show that after adding the third component phenytoin sodium, only a fraction of the initial concentration remains on the diluent surface. The rest of the

Fig. 3.38 The influence of mixing sequence in a ternary mix on p/b ratios of Na^+ and Mg^{2+} detected on diluent surface

Lactose concentration 95%; lubricant concentration 0.5% $^{w}/_{w}$

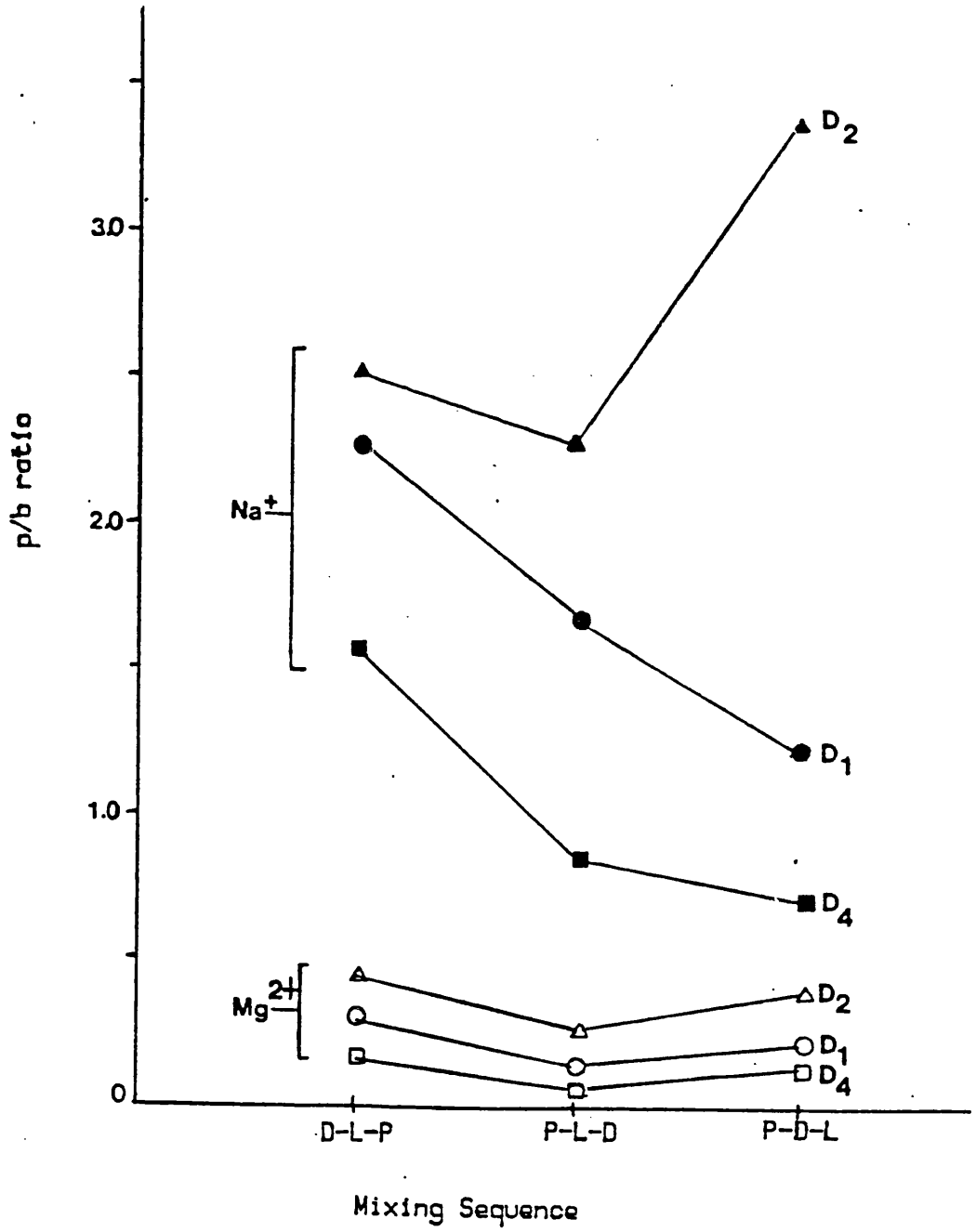


Table 3.15 p/b ratios of Na^+ and Mg^{2+} detected on diluent surfaces in various powder mixes

(values in brackets refer to standard deviation)

Powder Mix	Lactose D_1		Lactose D_2		Calcium sulphate dihydrate D_4	
	Na^+	Mg^{2+}	Na^+	Mg^{2+}	Na^+	Mg^{2+}
$P\text{-}D_{95\%}$	2.00 (0.40)	0.07 (0.05)	2.35 (0.52)	0.10 (0.05)	1.08 (0.35)	0.07 (0.04)
$P\text{-}D_{95\%}\text{-}L_{0.5\%}$	1.25 (0.32)	0.23 (0.16)	3.39 (0.65)	0.39 (0.08)	0.74 (0.29)	0.18 (0.07)
$P\text{-}L_{0.5\%}\text{-}D_{95\%}$	1.74 (0.31)	0.20 (0.31)	2.27 (0.78)	0.31 (0.08)	0.93 (0.55)	0.16 (0.06)
$D_{95\%}\text{-}L_{0.5\%}\text{-}P$	2.30 (0.60)	0.29 (0.81)	2.50 (0.84)	0.45 (0.09)	1.66 (0.75)	0.18 (0.07)
$D\text{-}L_{0.5\%}$	0.18 (0.14)	0.44 (0.11)	0.17 (0.06)	0.64 (0.12)	0.15 (0.09)	0.35 (0.07)

Table 3.16 Analysis of variance of the effect of mixing sequence and diluent type on the p/b ratio for Na^+ detected on diluent surface

Source of variation	Degrees of freedom	Sum of Squares	Mean Squares	Variance Ratio F
Mixing sequence	2	7.647	3.823	11.73 *
Diluent type	2	83.111	41.556	127.47 *
Interaction	4	25.380	6.345	19.46 *
Error	171	55.763	0.326	
Total	179	171.900		

* significant at 0.1% level

Table 3.17 Analysis of variance of the effect of mixing sequence and diluent type on the p/b ratio for Mg^{2+} present on diluent surface

Source of variation	Degrees of freedom	Sum of Squares	Mean Squares	Variance Ratio F
Mixing sequence	2	0.06111	0.03055	3.82 ‡
Diluent type	2	0.72300	0.36150	45.24 ⊕
Interaction	4	0.32057	0.08014	10.03 ⊕
Error	171	1.36609	0.00799	
Total	179	2.47077		

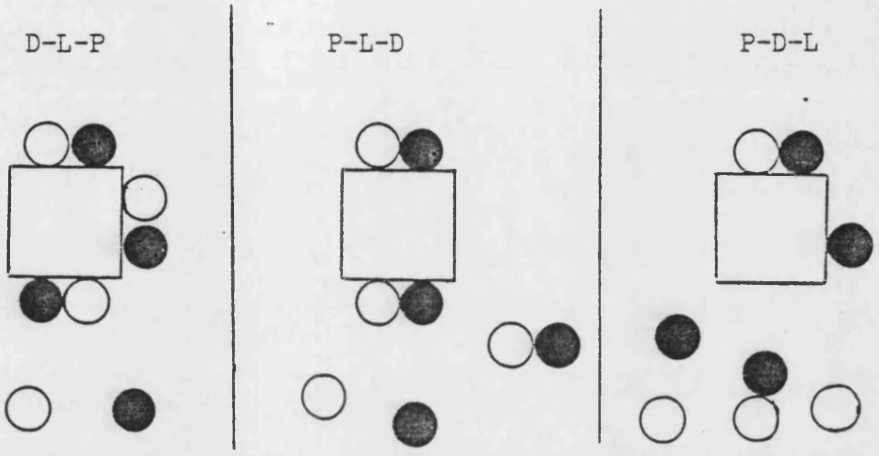
‡ Significant at 2.5% level

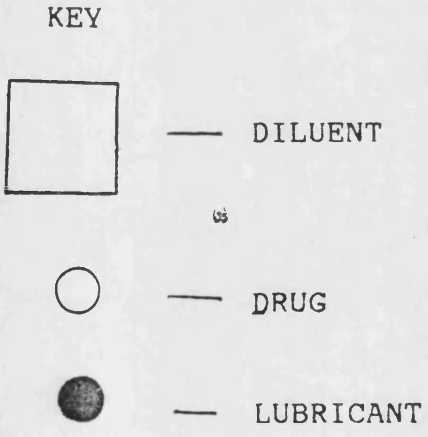
⊕ Significant at 0.1% level

lubricant may interact with free drug particles to form drug-lubricant units or is free within the mix. There was no significant difference ($p = 0.05\%$) between p/b ratios of Na^+ for three-component P-L-D mixes and two-component P-D mixes. However, p/b ratios of Na^+ in D-L-P mixes were much higher than those for the P-D mix. This suggests that ordered units of drug-lubricant, interacted with diluent to the same extent as drug particles alone, indicating that the partial coverage of lubricant on drug particles did not influence the ability of the drug to adhere to the diluent surface. However, a lubricant film on the diluent surface increased the tendency for drug to adhere to that surface (mixing sequence D-L-P). Thus referring to the two proposed mechanisms to explain the high levels of drug observed on the diluent surface for $P\text{-}D_2\text{-}L$ mixes (Fig. 3.37), it seems logical to conclude that though both mechanisms are likely to occur, the first mechanism (Scheme "1") probably predominates in the total mix. Lubricant levels on the diluent surface in P-D-L mixes were comparable to those in D-L-P mixes.

In terms of the spatial arrangement, D-L-P mixes will contain the lowest levels of both drug and lubricant existing as a random mix with ordered units of diluent - lubricant - drug particles. P-L-D mixes will contain the highest levels of free lubricant, which may interact with free drug particles. Finally, P-D-L mixes will contain the highest concentration of free drug particles when stripping of drug from diluent surface occurs. These effects are summarised schematically in Fig. 3.39.

Fig. 3.39 Schematic representation of the effect of mixing sequence on the spatial arrangement of the three components in systems containing drug, diluent and lubricant





3.4.2.3 Effect of diluent

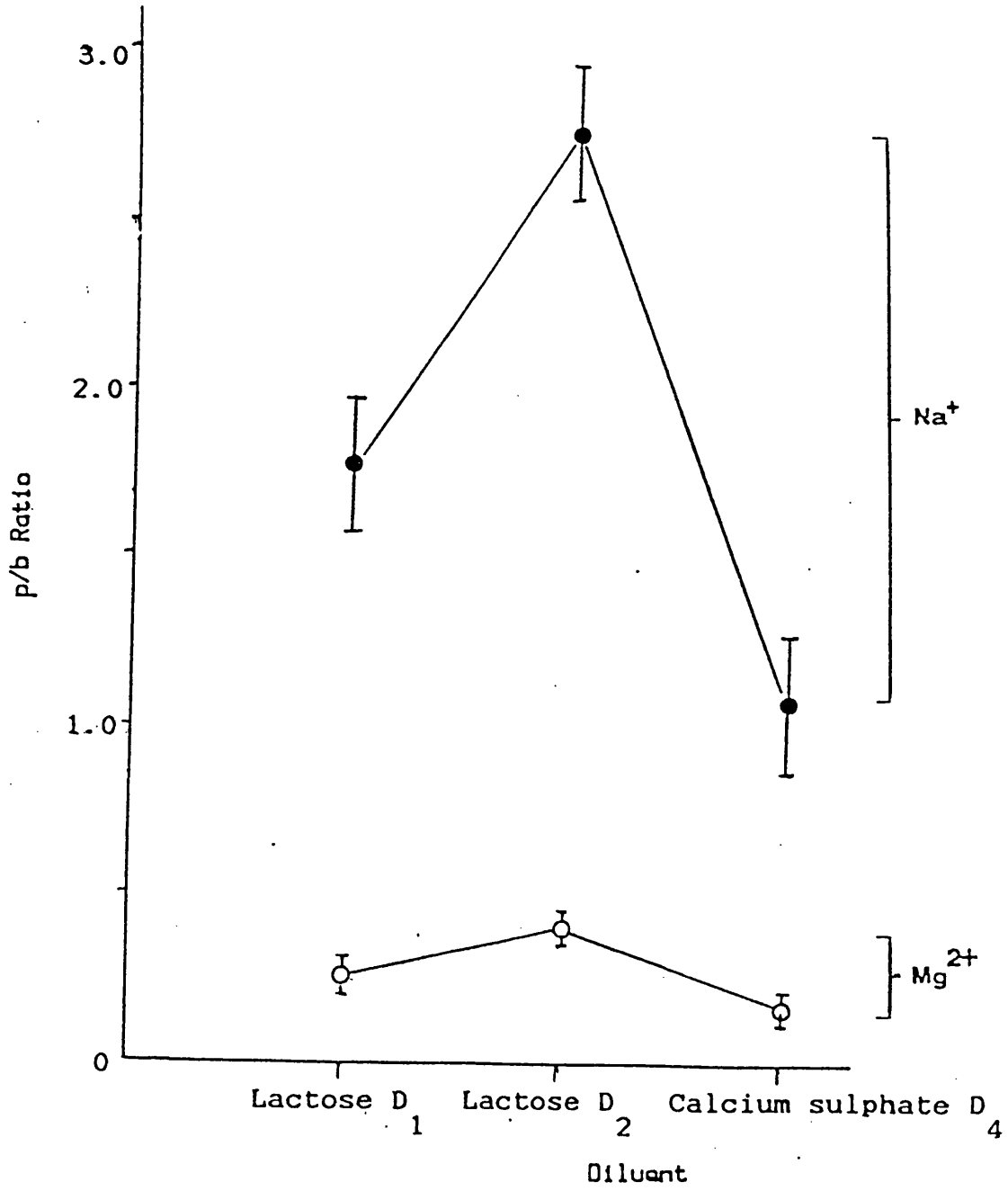
Fig. 3.40 shows the effect of diluent, type and source, on the amount of drug and lubricant adhering to the diluent surface. Lactose D_2 showed the highest levels of drug and lubricant and calcium sulphate D_4 the least.

The forces responsible for adhesion during pharmaceutical powder mixing are London-van der Waals, electrostatic forces and moisture bonding. Table 2.7 shows the mean specific charge developed on drug and excipient powders on contact with a metal surface. Phenytoin sodium and lactose D_2 developed electronegative charges whilst lactose D_1, calcium sulphate D_4 and magnesium stearate L_1 developed electropositive charges. For adhesion to occur opposite charges must attract, therefore it is unlikely that the electrostatic force was the primary force responsible for the high levels of drug observed on lactose D_2 surface. Moisture levels on the three diluents were comparable (Table 2.6) and so this also does not explain the trend observed. An examination of the surfaces of the diluents (Fig. 2.1) shows that lactose D_2 surfaces were porous whilst lactose D_1 and calcium sulphate D_4 were relatively smooth. Whatever the force responsible for adhesion, the crevices probably act as mechanical locking sites for the fine drug and lubricant particles.

Fig. 3.40 The influence of diluent, type and source, on p/b ratio of Na and Mg ions detected on diluent surface

(vertical bars refer to 95% confidence limits)

p/b ratios are mean values for all mixing sequences



3.5 GENERAL DISCUSSION - THE RELATION BETWEEN DISSOLUTION BEHAVIOUR AND SPATIAL DISTRIBUTION OF COMPONENTS ACHIEVED BY MIXING

For two-component powder mixes, it has been shown in Section 3.4.1.1, that there was an interaction during mixing between drug and diluent particles to form ordered units. There were significant differences in extent of interaction between drug and the different diluents D_1, D_2 or D_4. The drug concentrations used ($\geqslant 5\%$), were in excess of concentrations required to fully saturate the diluent surfaces and most of the drug particles were free within the mix and able to form separate agglomerates of the drug. The presence of diluent has been shown to generally retard dissolution rate (Section 3.2.2.2) therefore it will be expected that increased mutual distribution of drug and diluent particles should retard dissolution rate even further. As such one would expect dissolution rates from binary P-D_1 mixes to be higher than from P-D_2 mixes for comparable diluent particle sizes. This probably explains why dissolution rates for P-$D_{1(250\text{-}355\mu m)}$ (Fig. 3.16a) are higher than P-$D_{2(250\text{-}355\mu m)}$ (Fig. 3.16b). The effect will be more obvious in low dose preparations where drug concentrations less than 1% are used.

For three-component formulations containing magnesium stearate as lubricant, differences in the spatial arrangement of the components resulted in significant differences in dissolution rate. This was particularly obvious when the mixing sequence was varied (Fig. 3.22, 3.23, 3.24). For formulations prepared according to the mixing sequence D-L-P (Diluent - Lubricant - Phenytoin sodium), the dissolution rates are lower than those of the binary P-D mix. Thus although the presence of soluble diluents retarded dissolution rate, a hydrophobic

film on the diluent surface reduced the dissolution rate further. This is because the diluent used had a dual role in modifying dissolution behaviour. Its hydrophilic nature allows the penetration of aqueous fluid into the powder bed and its solubility and diffusion layer pH determine the amount of phenytoin that will be precipitated following initial dissolution. It is thus possible that a partial suppression of the rate of dissolution of diluent particles, whilst maintaining the hydrophilic nature of the diluent by virtue of only a partial coverage of diluent particles with lubricant, may cause the dissolution rates of D-L-P mixes to be higher than those of P-D mixes. At high diluent concentrations referred to as Phase 2 in Section 3.2.2.2, the dissolution rates are retarded to an even greater extent for formulations containing lactose D_2 and calcium sulphate D_4 (Fig. 3.23b, 3.24b). The results of semi-quantitative analysis of magnesium stearate on the surface of these diluents show that the amount of adhering lubricant was greatest for lactose D_2 and least for calcium sulphate D_4 (Fig. 3.38). A relatively insoluble diluent such as calcium sulphate, will be particularly sensitive to the presence of a hydrophobic film. Also the greater amount of lubricant on lactose D_2 as compared to lactose D_1, would explain why formulations of $D_{2(95\%)}$-L-P show a much lower dissolution rate than those of $D_{1(95\%)}$-L-P.

When increasing amounts of hydrophilic diluents are added to the P-L mix, to form a P-L-D mixing sequence, the dissolution rates are increased as would be expected. Dissolution rates in P-L-D mixes (Fig. 3.26) are lower than in P-D mixes due to the hydrophobic film formed on drug particles.

The results in Section 3.2.3.1 show that when up to 0.5% magnesium stearate is added to a binary mix containing 56.5% diluent in the sequence P-D-L, improved dissolution rates are observed. The result is thought to be a result of drug being stripped from diluent surface by the lubricant with a resultant increase in the concentration of "free" drug particles existing as aggregates with ordered units within the mix. When such a mix is encapsulated, drug particles are easily dispersed into dissolution medium once the capsule is penetrated by aqueous fluid. With an increase in lubricant levels, the adhesion of lubricant to both drug and diluent particles is increased. Also the concentration of lubricant in the total mix is increased, resulting in an overall increase in hydrophobicity of the mix and a decrease in dissolution rates.

When diluent levels in P-D mixes are increased above 56.5%, the proportion of drug adhering to diluent surface increases although the drug to diluent ratio in ordered units remain constant (Section 3.4.1.1). The addition of lubricant to such mixes will lead to stripping of drug with adhesion of lubricant to the diluent surface. It will be expected that dissolution rates for such mixes should be higher than those in the original P-D mixes. The fact that, in this case at higher diluent levels, dissolution rates are in general lower suggests that either there is an extensive interaction of lubricant with the diluent or that there is an overall increase in hydrophobicity of mix. Formulations containing lactose D_2 showed high levels of both drug and lubricant on diluent surface (Table 3.13). Such mixes showed poor dissolution behaviour as would be expected.

The toxicity observed in earlier studies (McQueen, 1968) when patients stabilised on formulations of phenytoin sodium were changed from calcium sulphate to those containing lactose has been explained as a conversion of the drug to an insoluble calcium complex (Bochner et al, 1972b; 1973). From the above discussions, other factors would also seem to have been involved. Tyrer et al (1970) reported that apart from the change in diluent, the manufacturers also increased the contents of magnesium stearate and magnesium silicate in the formulation. The increase in lubricant may have been expected to offset the improvement of dissolution rate which had been anticipated on changing the diluent. However, the changes would have resulted in changes in spatial distribution of the particles. From Fig. 3.40, powder mixes containing lactose show higher levels of both drug and lubricant on the diluent surface than corresponding mixes containing calcium sulphate dihydrate. When magnesium stearate is added to a partially ordered random drug-diluent mix, stripping of drug from diluent surface occurs. Since there is a greater interaction of the lubricant with lactose particles than with calcium sulphate, more drug particles are stripped off the lactose surface. The increased stripping of drug will mean more drug particles are free within the total mix. The present data show that, when such a mix is encapsulated and exposed to an aqueous medium, drug particles can disperse easily once the capsule is permeated by dissolution fluid.

4. CONCLUSIONS

4.1 CONCLUDING REMARKS

The release of phenytoin sodium from hard gelatin capsules containing particulate drug into an aqueous dissolution medium at pH 9.0 is fast and not influenced by either the drug particle size or the packing density. The effect is due in part to the high solubility of the sodium salt. It is also due to reactions which occur on contact of phenytoin sodium with aqueous medium. Phenytoin sodium is hygroscopic forming higher hydrates at high Relative Humidity. Evidence is presented to indicate that an expansion of the crystal lattice structure associated with hydration causes swelling of particles and powder bed packed in a capsule shell. As a result the dispersion of particles within the dissolution medium is facilitated and factors such as drug particle size and packing density are no longer rate-determining.

When diluents such as lactose or the less soluble calcium sulphate are added to phenytoin sodium, the drug release from capsules is generally retarded. The effect cannot however be predicted by considering the dissolution profiles at low and high diluent concentration. Both of these diluents were found to retard dissolution by facilitating the precipitation of the free insoluble acid form of the drug during dissolution. The extent of retardation appears to be associated with both the diluent solubility and, as would be expected the assumed pH of the diffusion layer around the diluent particles. Other factors such as prolonged storage of encapsulated powder mixes at ambient relative humidity, which promote the conversion of the salt to the free acid also retarded the dissolution rate of the drug. Formulations containing the more soluble diluent, lactose, were found to be particularly sensitive to storage conditions.

The influence of diluent particle size on dissolution from two-component formulations is thought to be related to the pore structure within the powder bed. Generally the larger the probable pore dimensions, the greater the ease of penetration of the dissolution medium and the subsequent rate of dissolution.

The effect of batch-to-batch variation in magnesium stearate on dissolution of phenytoin sodium from capsules could be correlated with the specific surface area of the lubricant. Capsule formulations containing lubricants having a high specific surface area showed slower dissolution.

During the mixing of the powders, there was an interaction between drug, diluent and lubricant particles to form partially ordered random mixes. The extent of interaction between drug and diluent or lubricant and diluent, depended on the chemical type of diluent and also on the source from which it was obtained. For two-component mixes increased interaction between drug and diluent particles resulted in slower dissolution. When magnesium stearate was present as a third component, the dissolution behaviour of the drug was greatly modified depending on the extent of interactions within the mix.

The adverse clinical effects observed in Australia when the diluent in phenytoin sodium capsules was changed from calcium sulphate to lactose has been attributed to the conversion of the drug to an insoluble calcium complex (Bochner et al, 1972b; 1973). The results obtained in the present study from in-vitro dissolution tests show no evidence of complexation. However, a number of other factors have been identified which may well have contributed to the Australian

incident. Capsules containing lactose in the absence of drug show a higher in-vitro dissolution rate than those of calcium sulphate because of the higher solubility of lactose. The presence of lactose certainly improved dissolution rate when the insoluble free acid form was precipitated during the early stages of a dissolution process. Also by changing the chemical form of the diluent and increasing the levels of lubricant in the formulation, changes in the spatial distribution of the components may have occurred. Lactose particles interact to a greater extent with both drug and lubricant particles than do calcium sulphate particles. Therefore, when magnesium stearate is added to a partially ordered binary mix of drug and diluent, greater numbers of drug particles may be stripped from the lactose surface than for corresponding mixes containing calcium sulphate as diluent. As a result such mixes containing lactose have higher concentrations of free drug within the mix which is easily dispersed when the capsule formulation is introduced into a dissolution medium.

The most common objective of powder mixing in the pharmaceutical industry is to obtain mutual distribution of formulation components such that a unit dose provides the patient with a reproducible quantity of active ingredient. Most solid dosage formulations consist of drug plus a number of excipients including diluent, disintegrant and lubricant. Where magnesium stearate is added to improve the flow and/or lubricity of the powder mix, the lubricant is commonly added at the end of the mixing operation. Mixing time is usually restricted such that the dissolution rate of the drug is not affected by extensive shearing of the particles to form a hydrophobic coating on the drug particles. Very little attention is paid to the overall spatial arrangement of particles. From the results presented in this thesis,

such factors should be considered in the design of solid dosage forms such as low dose preparations or other preparations where bioavailability problems related to dissolution are likely to occur.

4.2 SUGGESTIONS FOR FURTHER WORK

Further studies are needed to fully characterise the hydrates of phenytoin sodium. So far the crystalline structure of anhydrous phenytoin sodium has not been documented. The determination of the crystalline structure of the drug will allow more detailed understanding of the changes which occur on hydration. Also the use of thermogravimetric analysis (TGA) in conjunction with DSC will enable the loss in weight of water with each endothermic dehydration to be quantified.

The peak-to-background ratio has been successfully used in this small-scale study to analyse semi-quantitatively the spatial arrangement of components in powder mixes and to obtain evidence of interaction between particles. An extension of the work on mixing, to encompass larger-scale mixing processes, is necessary to confirm differences in spatial arrangement and to identify any additional effects due to scale-up of the mixing operation.

By the use of phenytoin sodium and magnesium stearate to prepare ordered mixes very low counts of ions were detected by X-ray analysis. This limited the statistical precision of the results that could be obtained. The use of fine particles such as NaCl or KCl as model drug compounds, for which the elemental concentration is high would improve the precision of such investigations.

Peak and background counts were obtained on integration using only the central channel of peak or the K_{α} channel for the various ions to obtain the mean count rate. This method gives a low statistical precision as the rest of the counts which contribute to the peak are wasted. As an alternative approach, the integration could be carried out over 99% of the peak area, though the computed p/b ratio would then

be lower due to the large number of background counts being included. The relative probability of overlap between neighbouring peaks would also be increased. A reasonable compromise might be to integrate over a region equivalent to 68% of the area under the normal curve. This would reduce variation in counts and also improve the precision within the experiment.

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